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(54) **ESTROGEN RECEPTOR MODULATORS**

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A61K 31/12 (2006.01)

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(58) **Field of Classification Search** None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to compounds and derivatives thereof, their synthesis, and their use as estrogen receptor modulators. The compounds of the instant invention are ligands for estrogen receptors and as such may be useful for treatment or prevention of a variety of conditions related to estrogen functioning including: bone loss, bone fractures, osteoporosis, metastatic bone disease, Paget's disease, periodontal disease, cartilage degeneration, endometriosis, uterine fibroid disease, hot flashes, increased levels of LDL cholesterol, cardiovascular disease, impairment of cognitive functioning, age-related mild cognitive impairment, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity, incontinence, inflammation, inflammatory bowel disease, irritable bowel syndrome, sexual dysfunction, hypertension, retinal degeneration and cancer, in particular of the breast, uterus and prostate.

14 Claims, No Drawings

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ESTROGEN RECEPTOR MODULATORS

PRIORITY CLAIM

This application is claims priority to US Provisional Application Ser. No. 60/623,910, filed on Nov. 1, 2004.

BACKGROUND OF THE INVENTION

Naturally occurring and synthetic estrogens have broad therapeutic utility, including: relief of menopausal symptoms, treatment of acne, treatment of dysmenorrhea and dysfunctional uterine bleeding, treatment of osteoporosis, treatment of hirsutism, treatment of prostatic cancer, treatment of hot flashes and prevention of cardiovascular disease. Because estrogen is very therapeutically valuable, there has been great interest in discovering compounds that mimic estrogen-like behavior in estrogen responsive tissues.

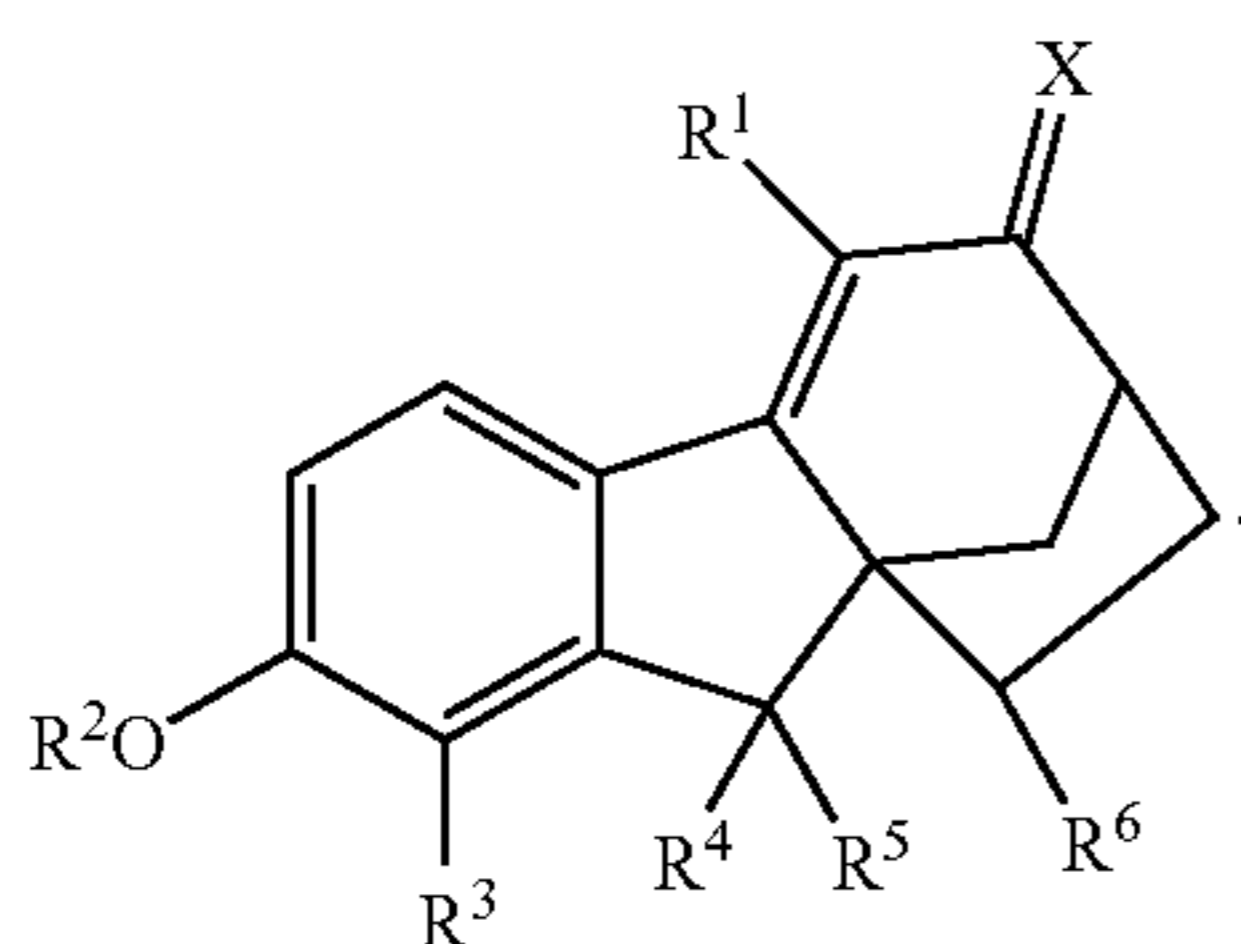
The estrogen receptor has been found to have two forms: ER α and ER β . Ligands bind differently to these two forms, and each form has a different tissue specificity to binding ligands. Thus, it is possible to have compounds that are selective for ER α or ER β , and therefore confer a degree of tissue specificity to a particular ligand.

What is needed in the art are compounds that can produce the same positive responses as estrogen replacement therapy without the negative side effects. Also needed are estrogen-like compounds that exert selective effects on different tissues of the body.

The compounds of the instant invention are ligands for estrogen receptors and as such may be useful for treatment or prevention of a variety of conditions related to estrogen functioning including: bone loss, bone fractures, osteoporosis, metastatic bone disease, Paget's disease, periodontal disease, cartilage degeneration, endometriosis, uterine fibroid disease, hot flashes, increased levels of LDL cholesterol, cardiovascular disease, impairment of cognitive functioning, age-related mild cognitive impairment, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity, incontinence, anxiety, depression resulting from an estrogen deficiency, inflammation, inflammatory bowel disease, irritable bowel syndrome, sexual dysfunction, hypertension, retinal degeneration and cancer, in particular of the breast, uterus and prostate.

SUMMARY OF THE INVENTION

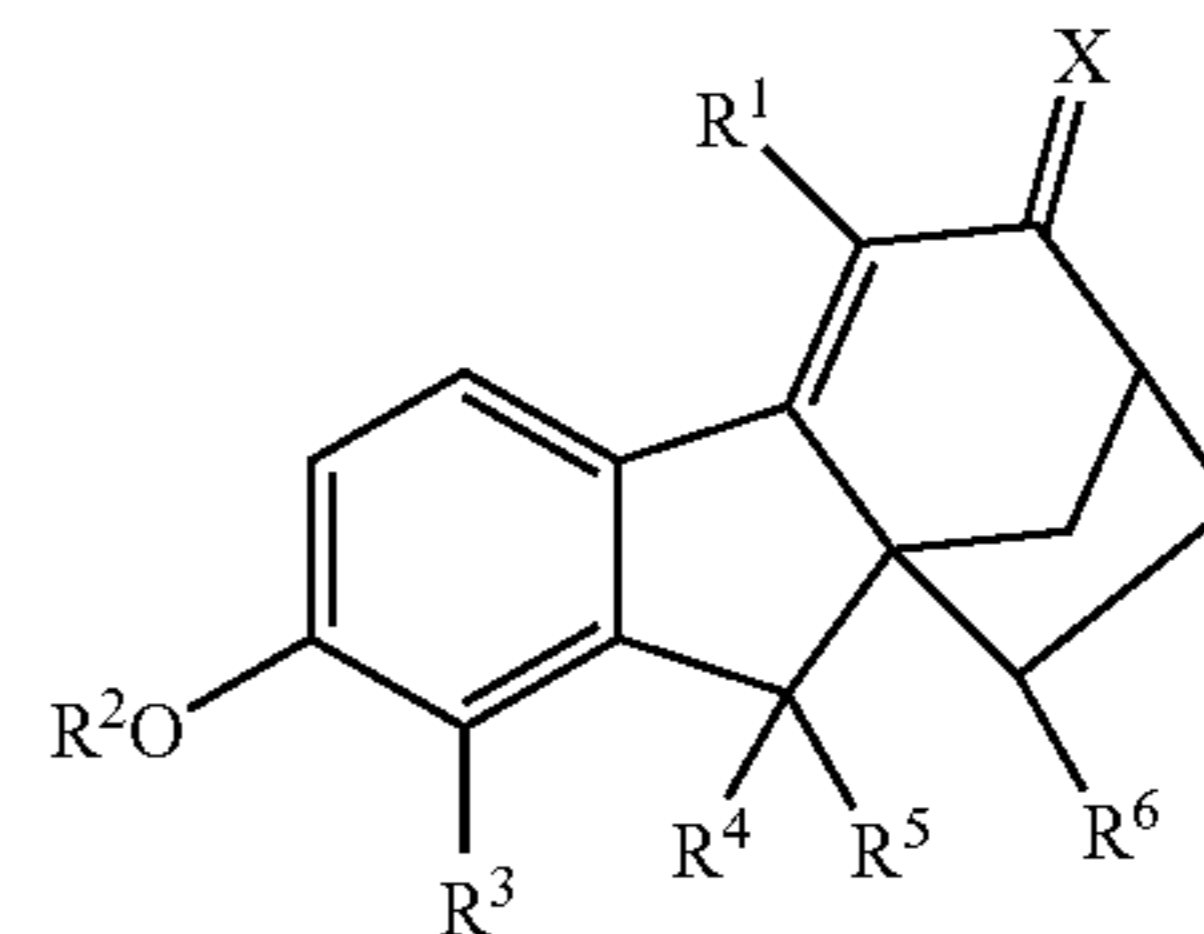
The present invention relates to compounds and pharmaceutical compositions useful for treating or preventing a variety of conditions related to estrogen functioning. One embodiment of the present invention is illustrated by treating or preventing estrogen related disorders with a compound of the following formula, and the pharmaceutically acceptable salts and stereoisomers thereof:



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DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds and pharmaceutical compositions useful for treating or preventing a variety of conditions related to estrogen functioning. One embodiment of the present invention is illustrated by a compound of the following formula, and the pharmaceutically acceptable salts and stereoisomers thereof:



wherein X is O, N—OR^a, N—N(R^a)₂, or C₁₋₆ alkylidene, wherein said alkylidene group is optionally substituted with hydroxyl, amino, O(C₁₋₄ alkyl), NH(C₁₋₄ alkyl) or N(C₁₋₄ alkyl)₂;

R¹ is fluoro, chloro, bromo, iodo, cyano, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, aryl, or heteroaryl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl groups are optionally substituted with one, two or three groups selected from the group consisting of fluoro, chloro, bromo, iodo, cyano and OR^a;

R² is hydrogen, R^a, (C=O)R^a or (C=O)OR^a;

R³ is hydrogen, fluoro, chloro, bromo, iodo, C₁₋₂ alkyl, cyano or OR^a;

R⁴ is hydrogen, fluoro, chloro, bromo or hydroxyl;

R⁵ is hydrogen, fluoro, chloro, bromo or hydroxyl;

Or R⁴ and R⁵, when taken together with the carbon atom to which they are attached, form a carbonyl group;

R⁶ is hydrogen, fluoro, chloro or C₁₋₅ alkyl, wherein said alkyl group is optionally substituted with a group selected from the group consisting of chloro, bromo, iodo, OR^a and 1-5 fluoro;

R^a is hydrogen, C₁₋₄ alkyl or phenyl, wherein said alkyl and phenyl groups are optionally substituted with a group selected from the group consisting of hydroxyl, amino, O(C₁₋₄ alkyl), NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)₂, chloro, bromo, 1-5 fluoro, iodo, cyano and OR^a; when two or more R^a groups are present, they are independently selected;

or a pharmaceutically acceptable salt or stereoisomer thereof.

In a class of the embodiment, X is O.

In a class of the embodiment, R¹ is fluoro, chloro, bromo, iodo, cyano, C₁₋₄ alkyl, or phenyl, wherein said alkyl and phenyl groups are optionally substituted with one, two or three groups selected from the group consisting of fluoro, chloro, bromo, iodo, cyano and OR^a. In a subclass of the embodiment, R¹ is chloro, bromo, cyano, methyl, ethyl or phenyl, wherein said methyl and phenyl groups are optionally substituted with one, two or three groups selected from the group consisting of fluoro, chloro and bromo.

In a class of the embodiment, R² is hydrogen.

In a class of the embodiment, R³ is hydrogen, fluoro, chloro, bromo or methyl.

In a class of the embodiment, R⁴ is hydrogen.

In a class of the embodiment, R⁵ is hydrogen.

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In a class of the embodiment, R⁶ is hydrogen or C₁₋₄ alkyl.
In a class of the embodiment, R^a is hydrogen.

Non-limiting examples of the present invention include, but are not limited to:

1,5-dichloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
2-hydroxy-5-methylgibba-1,3,4a(10a),4b-tetraen-6-one;
2-hydroxy-5-(trifluoromethyl)gibba-1,3,4a(10a),4b-tetraen-6-one;
2-hydroxy-6-oxogibba-1,3,4a(10a),4b-tetraene-5-carbonitrile;
5-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
5-bromo-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
5-chloro-2-hydroxy-1-methylgibba-1,3,4a(10a),4b-tetraen-6-one;
5-bromo-2-hydroxy-1-methylgibba-1,3,4a(10a),4b-tetraen-6-one;
5-chloro-1-fluoro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
5-bromo-1-fluoro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
5-bromo-1-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
1-chloro-2-hydroxy-5-methylgibba-1,3,4a(10a),4b-tetraen-6-one;
1-chloro-5-ethyl-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
1-chloro-2-hydroxy-6-oxogibba-1,3,4a(10a),4b-tetraene-5-carbonitrile;
1-chloro-2-hydroxy-5-phenylgibba-1,3,4a(10a),4b-tetraen-6-one;
1-bromo-5-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
1,5-dibromo-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
2-hydroxy-5-methyl-9-propylgibba-1,3,4a(10a),4b-tetraen-6-one;
1,5-dichloro-2-hydroxygibba-1,3,4a(10a),4b-tetraene-6,10-dione;
1-chloro-5-ethyl-2-hydroxygibba-1,3,4a(10a),4b-tetraene-6,10-dione;
1,5-dichloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one oxime;
(7beta,9alpha)-1,5-dichloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
(7beta,9alpha)-2-hydroxy-5-methylgibba-1,3,4a(10a),4b-tetraen-6-one;
(7beta,9alpha)-2-hydroxy-5-(trifluoromethyl)gibba-1,3,4a(10a),4b-tetraen-6-one;
(7beta,9alpha)-2-hydroxy-6-oxogibba-1,3,4a(10a),4b-tetraene-5-carbonitrile;
(7beta,9alpha)-5-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
(7beta,9alpha)-5-bromo-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
(7beta,9alpha)-5-chloro-2-hydroxy-1-methylgibba-1,3,4a(10a),4b-tetraen-6-one;
(7beta,9alpha)-5-bromo-2-hydroxy-1-methylgibba-1,3,4a(10a),4b-tetraen-6-one;
(7beta,9alpha)-5-chloro-1-fluoro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
(7beta,9alpha)-5-bromo-1-fluoro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
(7beta,9alpha)-5-bromo-1-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
(7beta,9alpha)-2-chloro-2-hydroxy-5-methylgibba-1,3,4a(10a),4b-tetraen-6-one;
(7beta,9alpha)-1-chloro-5-ethyl-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

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(7beta,9alpha)-1-chloro-2-hydroxy-6-oxogibba-1,3,4a(10a),4b-tetraene-5-carbonitrile;
(7beta,9alpha)-1-chloro-2-hydroxy-5-phenylgibba-1,3,4a(10a),4b-tetraen-6-one;
5 (7beta,9alpha)-1-bromo-5-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
(7beta,9alpha)-1,5-dibromo-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;
(7beta,9alpha)-2-hydroxy-5-methyl-9-propylgibba-1,3,4a(10a),4b-tetraen-6-one;
10 (7beta,9alpha)-1,5-dichloro-2-hydroxygibba-1,3,4a(10a),4b-tetraene-6,10-dione;
(7beta,9alpha)-1-chloro-5-ethyl-2-hydroxygibba-1,3,4a(10a),4b-tetraene-6,10-dione;
15 (7beta,9alpha)-1,5-dichloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one oxime;

and the pharmaceutically acceptable salts thereof.

Also included within the scope of the present invention is a pharmaceutical composition which is comprised of a compound as described above and a pharmaceutically acceptable carrier. The invention is also contemplated to encompass a pharmaceutical composition which is comprised of a pharmaceutically acceptable carrier and any of the compounds specifically disclosed in the present application. The present invention also relates to methods for making the pharmaceutical compositions of the present invention. The present invention is also related to processes and intermediates useful for making the compounds and pharmaceutical compositions of the present invention. These and other aspects of the invention will be apparent from the teachings contained herein.

Utilities

The compounds of the present invention are selective modulators of estrogen receptors and are therefore useful to treat or prevent a variety of diseases and conditions related to estrogen receptor functioning in mammals, preferably humans.

The compounds of the present invention have advantages over similar compounds known in the art in that they present a more desirable metabolic profile. Drug metabolism can be observed in vitro in human liver microsome assays, see e.g., Regina W. Wang, "Validation of (-)-N-3-benzyl-phenobarbital as a selective inhibitor of CYP2C19 in human liver microsomes," DMD 32:584-586, 2004.

A variety of diseases and conditions related to estrogen receptor functioning includes, but is not limited to, bone loss, bone fractures, osteoporosis, metastatic bone disease, Paget's disease, periodontal disease, cartilage degeneration, endometriosis, uterine fibroid disease, hot flashes, increased levels of LDL cholesterol, cardiovascular disease, impairment of cognitive functioning, age-related mild cognitive impairment, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity, incontinence, anxiety, depression resulting from an estrogen deficiency, perimenopausal depression, post-partum depression, premenstrual syndrome, manic depression, dementia, obsessive compulsive behavior, attention deficit disorder, sleep disorders, irritability, impulsivity, anger management, multiple sclerosis and Parkinson's disease, inflammation, inflammatory bowel disease, irritable bowel syndrome, sexual dysfunction, hypertension, retinal degeneration and cancer, in particular of the breast, uterus and prostate. In treating such conditions with the instantly claimed compounds, the required therapeutic amount will vary according to the specific disease and is readily ascertainable by those skilled in the art. Although both treatment

and prevention are contemplated by the scope of the invention, the treatment of these conditions is the preferred use.

The present invention also relates to methods for eliciting an estrogen receptor modulating effect in a mammal in need thereof by administering the compounds and pharmaceutical compositions of the present invention.

The present invention also relates to methods for eliciting an estrogen receptor antagonizing effect in a mammal in need thereof by administering the compounds and pharmaceutical compositions of the present invention. The estrogen receptor antagonizing effect can be either an ER α antagonizing effect, an ER β antagonizing effect or a mixed ER α and ER β antagonizing effect.

The present invention also relates to methods for eliciting an estrogen receptor agonizing effect in a mammal in need thereof by administering the compounds and pharmaceutical compositions of the present invention. The estrogen receptor agonizing effect can be either an ER α agonizing effect, an ER β agonizing effect or a mixed ER α and ER β agonizing effect. A preferred method of the present invention is eliciting an ER β agonizing effect.

The present invention also relates to methods for treating or preventing disorders related to estrogen functioning, bone loss, bone fractures, osteoporosis, metastatic bone disease, Paget's disease, periodontal disease, cartilage degeneration, endometriosis, uterine fibroid disease, hot flashes, increased levels of LDL cholesterol, cardiovascular disease, impairment of cognitive functioning, age-related mild cognitive impairment, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity, incontinence, anxiety, depression resulting from an estrogen deficiency, inflammation, inflammatory bowel disease, irritable bowel syndrome, sexual dysfunction, hypertension, retinal degeneration and cancer, in particular of the breast, uterus and prostate in a mammal in need thereof by administering the compounds and pharmaceutical compositions of the present invention. Exemplifying the invention is a method of treating or preventing depression. Exemplifying the invention is a method of treating or preventing anxiety. Exemplifying the invention is a method of treating or preventing hot flashes. Exemplifying the invention is a method of treating or preventing cancer, in particular of the breast, uterus and prostate. Exemplifying the invention is a method of treating or preventing cardiovascular disease.

An embodiment of the invention is a method for treating or preventing cancer, especially of the breast, uterus or prostate, in a mammal in need thereof by administering the compounds and pharmaceutical compositions of the present invention. The utility of SERMs for the treatment of breast, uterine or prostate cancer is known in the literature, see T. J. Powles, "Breast cancer prevention," *Oncologist* 2002; 7(1): 604; Park, W. C. and Jordan, V. C., "Selective estrogen receptor modulators (SERMs) and their roles in breast cancer prevention," *Trends Mol Med.* 2002 February; 8(2): 82-8; Wolff, A. C. et al., "Use of SERMs for the adjuvant therapy of early-stage breast cancer," *Ann N Y Acad Sci.* 2001 December; 949:80-8; Hou, Y. F. et al., "ERbeta exerts multiple stimulative effects on human breast carcinoma cells," *Oncogene* 2004 Jul. 29; 23(34):5799-806; Steiner, M. S. et al., "Selective estrogen receptor modulators for the chemoprevention of prostate cancer," *Urology* 2001 April; 57(4 Suppl 1):68-72; Lai, J. S. et al., "Metastases of prostate cancer express estrogen receptor beta," *Urology* 2004 October; 64(4):814-20; Imamov, O., et al., "Estrogen receptor β in prostate cancer," *N Engl J Med* 351;26, 2773-2274; Koehler, K., et al., "Reflections on the Discovery and Significance of Estrogen Receptor β ," *Endocrine Reviews*, May

2005, 26(3):465-478; Neubauer, et al., "The Selective Estrogen Receptor Modulator Trioxifene (LY33314) Inhibits Metastasis and Extends Survival in the P4III Rat Prostatic Carcinoma Model," *Cancer Research* 63, 6056-6062, Sep. 15, 2003.

Another embodiment of the invention is a method of treating or preventing metastatic bone disease in a mammal in need thereof by administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. The utility of SERMs in the treatment of metastatic bone disease is known in the literature, see, Campisi, C. et al., "Complete resolution of breast cancer bone metastasis through the use of beta-interferon and tamoxifen," *Eur J Gynaecol Oncol* 1993; 14(6):479-83.

Another embodiment of the invention is a method of treating or preventing hot flashes in a mammal in need thereof by administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. The utility of SERMs in the treatment of hot flashes has been discussed in the literature, see, Seidlova-Wuttke D., et al., "Belamcanda chinensis and the thereof purified tectorigenin have selective estrogen receptor modulator activities," *Phytomedicine.* 2004 July; 11(5):392-403.

Another embodiment of the invention is a method of treating or preventing gynecomastia in a mammal in need thereof by administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. The utility of SERMs in the treatment of gynecomastia is known in the literature, see, Ribeiro, G. and Swindell R., "Adjuvant tamoxifen for male breast cancer." *Br J Cancer* 1992; 65:252-254; Donegan, W., "Cancer of the Male Breast," *JGSM* Vol. 3, Issue 4, 2000.

Another embodiment of the invention is a method of treating or preventing post-menopausal osteoporosis, glucocorticoid osteoporosis, hypercalcemia of malignancy, bone loss and bone fractures in a mammal in need thereof by administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. The utility of SERMs to treat or prevent osteoporosis, hypercalcemia of malignancy, bone loss or bone fractures is known in the literature, see Jordan, V. C. et al., "Selective estrogen receptor modulation and reduction in risk of breast cancer, osteoporosis and coronary heart disease," *Natl Cancer Inst* 2001 October; 93(19): 1449-57; Bjarnason, N H et al., "Six and twelve month changes in bone turnover are related to reduction in vertebral fracture risk during 3 years of raloxifene treatment in postmenopausal osteoporosis," *Osteoporosis Int* 2001; 12(11):922-3; Fentiman, I. S., "Tamoxifen protects against steroid-induced bone loss," *Eur J Cancer* 28:684-685 (1992); Rodan, G. A. et al., "Therapeutic Approaches to Bone Diseases," *Science* Vol 289, 1 Sep. 2000.

Another embodiment of the invention is a method of treating or preventing periodontal disease or tooth loss in a mammal in need thereof by administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. The use of SERMs to treat periodontal disease or tooth loss in a mammal is known in the literature, see Rodan, G. A. et al., "Therapeutic Approaches to Bone Diseases," *Science* Vol 289, 1 Sep. 2000 pp. 1508-14.

Another embodiment of the invention is a method of treating or preventing Paget's disease in a mammal in need thereof by administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical

compositions described above. The use of SERMs to treat Paget's disease in a mammal is known in the literature, see Rodan, G. A. et al., "Therapeutic Approaches to Bone Diseases," *Science* Vol 289, 1 Sep. 2000 pp. 1508–14.

Another embodiment of the invention is a method of treating or preventing uterine fibroid disease in a mammal in need thereof by administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. The use of SERMs to treat uterine fibroids, or uterine leiomyomas, is known in the literature, see Palomba, S., et al., "Effects of raloxifene treatment on uterine leiomyomas in postmenopausal women," *Fertil Steril.* 2001 July; 76(1):3843.

Another embodiment of the invention is a method of treating or preventing obesity in a mammal in need thereof by administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. The use of SERMs to treat obesity is known in the literature, see Picard, F. et al., "Effects of the estrogen antagonist EM-652.HCl on energy balance and lipid metabolism in ovariectomized rats," *Int J Obes Relat Metab Disord.* 2000 July; 24(7):830–40.

Another embodiment of the invention is a method of treating or preventing cartilage degeneration, rheumatoid arthritis or osteoarthritis in a mammal in need thereof by administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. The use of SERMs to treat cartilage degeneration, rheumatoid arthritis or osteoarthritis is known in the literature, see Badger, A. M. et al., "Idoxifene, a novel selective estrogen receptor modulator, is effective in a rat model of adjuvant-induced arthritis." *J Pharmacol Exp Ther.* 1999 December; 291(3): 1380–6.

Another embodiment of the invention is a method of treating or preventing endometriosis in a mammal in need thereof by administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. The use of SERMs to treat endometriosis is known in the art, see Steven R. Goldstein, "The Effect of SERMs on the Endometrium," *Annals of the New York Academy of Sciences* 949:237–242 (2001).

Another embodiment of the invention is a method of treating or preventing urinary incontinence in a mammal in need thereof by administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. The use of SERMs to treat urinary incontinence is known in the art, see, Goldstein, S. R., "Raloxifene effect on frequency of surgery for pelvic floor relaxation," *Obstet Gynecol.* 2001 July; 98(1):91–6.

Another embodiment of the invention is a method of treating or preventing cardiovascular disease, restenosis, lowering levels of LDL cholesterol and inhibiting vascular smooth muscle cell proliferation in a mammal in need thereof by administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. Estrogen appears to have an effect on the biosynthesis of cholesterol and cardiovascular health. Statistically, the rate of occurrence of cardiovascular disease is roughly equal in postmenopausal women and men; however, premenopausal women have a much lower incidence of cardiovascular disease than men. Because postmenopausal women are estrogen deficient, it is believed that estrogen plays a beneficial role in preventing cardiovascular disease. The mechanism is not well understood, but evidence indicates that estrogen can upregulate the low density lipid (LDL) cholesterol receptors in the liver to remove

excess cholesterol. The utility of SERMs in treating or preventing cardiovascular disease, restenosis, lowering levels of LDL cholesterol and inhibiting vascular smooth muscle cell proliferation is known in the art, see Nuttall, M E et al., "Idoxifene: a novel selective estrogen receptor modulator prevents bone loss and lowers cholesterol levels in ovariectomized rats and decreases uterine weight in intact rats," *Endocrinology* 1998 December; 139(12):5224–34; Jordan, V. C. et al., "Selective estrogen receptor modulation and reduction in risk of breast cancer, osteoporosis and coronary heart disease," *Natl Cancer Inst* 2001 October; 93(19):1449–57; Guzzo J A., "Selective estrogen receptor modulators—a new age of estrogens in cardiovascular disease?," *Clin Cardiol* 2000 January; 23(1): 15–7; Simoncini T, Genazzani A R., "Direct vascular effects of estrogens and selective estrogen receptor modulators," *Curr Opin Obstet Gynecol* 2000 June; 12(3): 181–7.

Another embodiment of the invention is a method of treating or preventing the impairment of cognitive functioning, age-related mild cognitive impairment, or cerebral degenerative disorders in a mammal in need thereof by administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. In models, estrogen has been shown to have beneficial effects on cognitive functioning, such as relieving anxiety and depression and treating or preventing Alzheimer's disease. Estrogen affects the central nervous system by increasing cholinergic functioning, neurotrophin and neurotrophin receptor expression. Estrogen also increases glutamergic synaptic transmission, alters amyloid precursor protein processing and provides neuroprotection. Thus, the estrogen receptor modulators of the present invention could be beneficial for improving cognitive functioning or treating age-related mild cognitive impairment, attention deficit disorder, sleep disorders, irritability, impulsivity, anger management, multiple sclerosis and Parkinsons disease. See, Sawada, H and Shimohama, S, "Estrogens and Parkinson disease: novel approach for neuroprotection," *Endocrine.* 2003 June; 21(1):77–9; McCullough L D, and Hurn, P D, "Estrogen and ischemic neuroprotection: an integrated view," *Trends Endocrinol Metab.* 2003 July; 14(5):228–35; which are hereby incorporated by reference in their entirety. The utility of SERMs to prevent the impairment of cognitive functioning is known in the art, see Yaffe, K., K. Krueger, S. Sarkar, et al. 2001, "Cognitive function in postmenopausal women treated with raloxifene," *N. Eng. J. Med.* 344: 1207–1213.

Another embodiment of the invention is a method of treating or preventing depression in a mammal in need thereof by administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. The utility of estrogens to prevent depression has been described in the art, see Carranza-Liram S., Valentino-Figueroa M L, "Estrogen therapy for depression in postmenopausal women," *Int J Gynaecol Obstet* 1999 April; 65(1):35–8. Specifically, estrogen receptor beta (ER β) selective agonists would be useful in the treatment of anxiety or depressive illness, including depression, perimenopausal depression, post-partum depression, premenstrual syndrome, manic depression, anxiety, dementia, and obsessive compulsive behavior, as either a single agent or in combination with other agents. Clinical studies have demonstrated the efficacy of the natural estrogen, 17 β -estradiol, for the treatment of various forms of depressive illness, see Schmidt P J, Nieman L, Danaceau M A, Tobin M B, Roca C A, Murphy J H, Rubinow D R, "Estrogen replacement in perimenopause-related depres-

sion: a preliminary report,” *Am J Obstet Gynecol* 183: 414–20, 2000; and Soares C N, Almeida O P, Joffe H, Cohen L S, “Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial,” *Arch Gen Psychiatry*. 58:537–8, 2001; which are hereby incorporated by reference. Bethea et al (Lu N Z, Shlaes T A, Gundlach C, Dziennis S E, Lyle R E, Bethea C L, “Ovarian steroid action on tryptophan hydroxylase protein and serotonin compared to localization of ovarian steroid receptors in midbrain of guinea pigs,” *Endocrine* 11:257–67, 1999, which is hereby incorporated by reference, have suggested that the antidepressant activity of estrogen may be mediated via regulation of serotonin synthesis in the serotonin containing cells concentrated in the dorsal raphe nucleus.

Another embodiment of the invention is a method of treating or preventing anxiety in a mammal in need thereof by administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. The contribution of estrogen receptors in the modulation of emotional processes, such as anxiety has been described in the art, see Krezel, W., et al., “Increased anxiety and synaptic plasticity in estrogen receptor beta-deficient mice,” *Proc Natl Acad Sci USA* 2001 Oct. 9; 98 (21): 12278–82.

Another embodiment of the invention is a method of treating or preventing inflammation, inflammatory bowel disease or irritable bowel syndrome. Inflammatory bowel diseases, including Crohn’s Disease and ulcerative colitis, are chronic disorders in which the intestine (bowel) becomes inflamed, often causing recurring abdominal cramps and diarrhea. The use of estrogen receptor modulators to treat inflammation and inflammatory bowel disease has been described in the art, see Harris, H. A. et al., “Evaluation of an Estrogen Receptor- β Agonist in Animal Models of Human Disease,” *Endocrinology*, Vol. 144, No. 10 4241–4249.

Another embodiment of the invention is a method of treating or preventing hypertension. Estrogen receptor beta has been reported to have a role in the regulation of vascular function and blood pressure, see Zhu, et al., “Abnormal Vascular Function and Hypertension in Mice Deficient in Estrogen Receptor β ,” *Science*, Vol 295, Issue 5554, 505–508, 18 Jan. 2002.

Another embodiment of the invention is a method of treating or preventing sexual dysfunction in males or females. The use of estrogen receptor modulators to treat sexual dysfunction has been described in the art, see Baulieu, E. et al, “Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: Contribution of the DHEAge Study to a sociobiomedical issue,” *PNAS*, Apr. 11, 2000, Vol. 97, No. 8, 4279–4282; Spark, Richard F., “Dehydroepiandrosterone: a springboard hormone for female sexuality,” *Fertility and Sterility*, Vol. 77, No. 4, Suppl 4, April 2002, S19–25.

Another embodiment of the invention is a method of treating or preventing retinal degeneration. Estrogen has been shown to have a beneficial effect of reducing the risk of advanced types of age-related maculopathy, see Snow, K. K., et al., “Association between reproductive and hormonal factors and age-related maculopathy in postmenopausal women,” *American Journal of Ophthalmology*, Vol. 134, Issue 6, December 2002, pp. 842–48.

Exemplifying the invention is the use of any of the compounds described above in the preparation of a medicament for the treatment or prevention of bone loss, bone fractures, osteoporosis, metastatic bone disease, Paget’s disease, periodontal disease, cartilage degeneration,

endometriosis, uterine fibroid disease, hot flashes, cardiovascular disease, impairment of cognitive functioning, age-related mild cognitive impairment, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity, incontinence, anxiety, depression, perimenopausal depression, post-partum depression, premenstrual syndrome, manic depression, dementia, obsessive compulsive behavior, attention deficit disorder, sleep disorders, irritability, impulsivity, anger management, multiple sclerosis and Parkinson’s disease, inflammation, inflammatory bowel disease, irritable bowel syndrome, sexual dysfunction, hypertension, retinal degeneration, an estrogen dependent cancer or prostate cancer, in a mammal in need thereof.

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

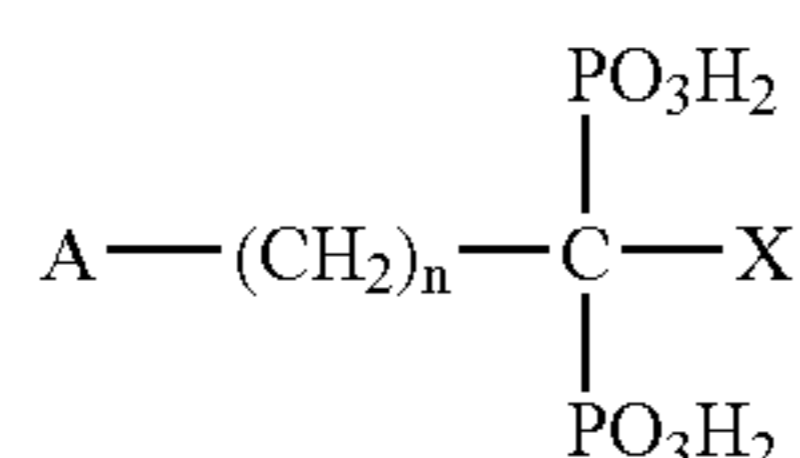
In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. For oral use of a therapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. For oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxy-ethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polyactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

The instant compounds are also useful in combination with known agents useful for treating or preventing bone loss, bone fractures, osteoporosis, metastatic bone disease, Paget's disease, periodontal disease, cartilage degeneration, endometriosis, uterine fibroid disease, hot flashes, increased levels of LDL cholesterol, cardiovascular disease, impairment of cognitive functioning, age-related mild cognitive impairment, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity, incontinence, anxiety, depression resulting from an estrogen deficiency, inflammation, inflammatory bowel disease, irritable bowel syndrome, sexual dysfunction, hypertension, retinal degeneration and cancer, in particular of the breast, uterus and prostate. Combinations of the presently disclosed compounds with other agents useful in treating or preventing the disorders disclosed herein are within the scope of the invention. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the disease involved. Such agents include the following: an organic bisphosphonate; a cathepsin K inhibitor; an estrogen or an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent, such as PTH; calcitonin; Vitamin D or a synthetic Vitamin D analogue; selective serotonin reuptake inhibitors (SSRIs); an aromatase inhibitor; and the pharmaceutically acceptable salts and mixtures thereof. A preferred combination is a compound of the present invention and an organic bisphosphonate. Another preferred combination is a compound of the present invention and a cathepsin K inhibitor. Another preferred combination is a compound of the present invention and an estrogen. Another preferred combination is a compound of the present invention and an androgen receptor modulator. Another preferred combination is a compound of the present invention and an osteoblast anabolic agent.

"Organic bisphosphonate" includes, but is not limited to, compounds of the chemical formula



wherein n is an integer from 0 to 7 and wherein A and X are independently selected from the group consisting of H, OH, halogen, NH₂, SH, phenyl, C₁₋₃₀ alkyl, C₃₋₃₀ branched or

cycloalkyl, bicyclic ring structure containing two or three N, C₁₋₃₀ substituted alkyl, C₁₋₁₀ alkyl substituted NH₂, C₃₋₁₀ branched or cycloalkyl substituted NH₂, C₁₋₁₀ dialkyl substituted NH₂, C₁₋₁₀ alkoxy, C₁₋₁₀ alkyl substituted thio, thiophenyl, halophenylthio, C₁₋₁₀ alkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazolyl, imidazopyridinyl, and benzyl, such that both A and X are not selected from H or OH when n is 0; or A and X are taken together with the carbon atom or atoms to which they are attached to form a C₃₋₁₀ ring.

In the foregoing chemical formula, the alkyl groups can be straight, branched, or cyclic, provided sufficient atoms are selected for the chemical formula. The C₁₋₃₀ substituted alkyl can include a wide variety of substituents, nonlimiting examples which include those selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazolyl, NH₂, C₁₋₁₀ alkyl or dialkyl substituted NH₂, OH, SH, and C₁₋₁₀ alkoxy.

The foregoing chemical formula is also intended to encompass complex carbocyclic, aromatic and hetero atom structures for the A or X substituents, nonlimiting examples of which include naphthyl, quinolyl, isoquinolyl, adamantyl, and chlorophenylthio.

Pharmaceutically acceptable salts and derivatives of the bisphosphonates are also useful herein. Non-limiting examples of salts include those selected from the group consisting alkali metal, alkaline metal, ammonium, and mono-, di-, tri-, or tetra-C₁₋₃₀ alkyl-substituted ammonium. Preferred salts are those selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts. More preferred are sodium salts. Non-limiting examples of derivatives include those selected from the group consisting of esters, hydrates, and amides.

It should be noted that the terms "bisphosphonate" and "bisphosphonates", as used herein in referring to the therapeutic agents of the present invention are meant to also encompass diphosphonates, biphosphonic acids, and diphosphonic acids, as well as salts and derivatives of these materials. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit the scope of the present invention, unless specifically indicated.

Nonlimiting examples of bisphosphonates include alendronate, cimadronate, clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate, and zolendronate, and pharmaceutically acceptable salts and esters thereof. A particularly preferred bisphosphonate is alendronate, especially a sodium, potassium, calcium, magnesium or ammonium salt of alendronic acid. Exemplifying the preferred bisphosphonate is a sodium salt of alendronic acid, especially a hydrated sodium salt of alendronic acid. The salt can be hydrated with a whole number of moles of water or non whole numbers of moles of water. Further exemplifying the preferred bisphosphonate is a hydrated sodium salt of alendronic acid, especially when the hydrated salt is alendronate monosodium trihydrate.

The precise dosage of the organic bisphosphonate will vary with the dosing schedule, the particular bisphosphonate chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the disorder to be treated, and other relevant medical and physical factors. For humans, an effective oral dose of bisphosphonate is typically from about 1.5 to about 6000 µg/kg body weight and preferably about 10 to about 2000 µg/kg of body weight. In alternative dosing regimens, the bisphosphonate can be administered at intervals other than daily, for example once-weekly dosing,

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twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In a once weekly dosing regimen, alendronate monosodium trihydrate would be administered at dosages of 35 mg/week or 70 mg/week. The bisphosphonates may also be administered monthly, ever six months, yearly or even less frequently, see WO 01/97788 (published Dec. 27, 2001) and WO 01/89494 (published Nov. 29, 2001).

“Estrogen” includes, but is not limited to naturally occurring estrogens [7-estradiol (E_2), estrone (E_1), and estriol (E_3)], synthetic conjugated estrogens, oral contraceptives and sulfated estrogens. See, Gruber C J, Tschugguel W, Schneeberger C, Huber J C., “Production and actions of estrogens” *N Engl J Med* 2002 Jan. 31; 346(5):340–52.

“Estrogen receptor modulators” refers to compounds which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, estrogen, progestogen, estradiol, droloxifene, raloxifene, lasofoxifene, TSE-424, tamoxifen, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl)]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

“Cathepsin K inhibitors” refers to compounds which interfere with the activity of the cysteine protease cathepsin K. Nonlimiting examples of cathepsin K inhibitors can be found in PCT publications WO 00/55126 to Axys Pharmaceuticals and WO 01/49288 to Merck Frosst Canada & Co. and Axys Pharmaceuticals.

“Androgen receptor modulators” refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α -reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

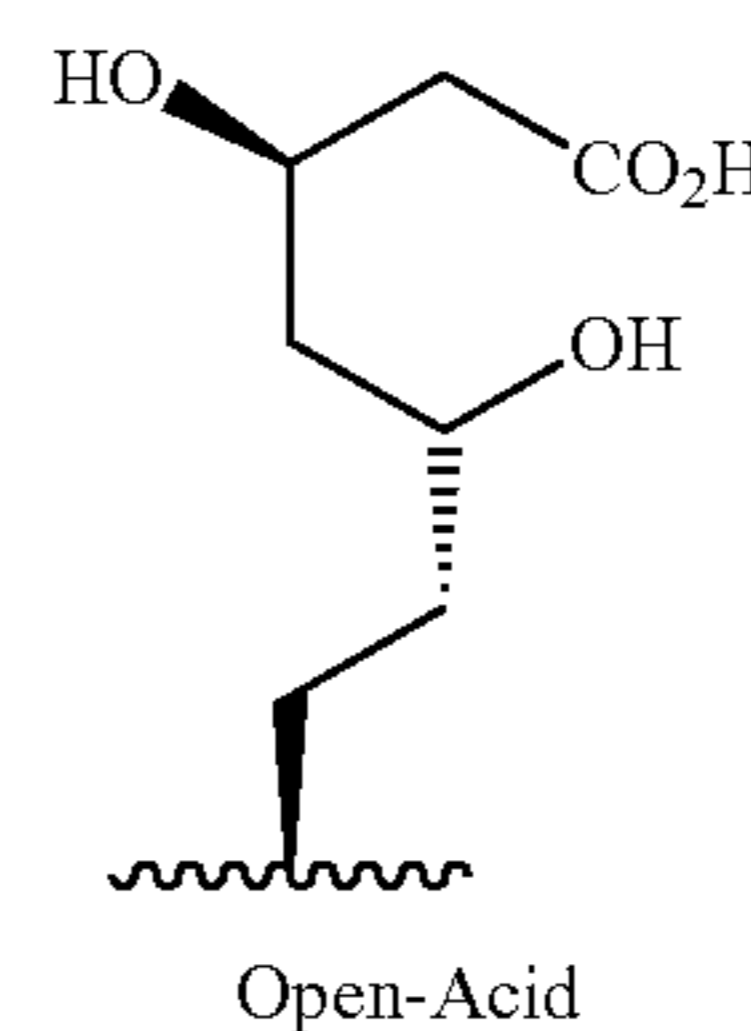
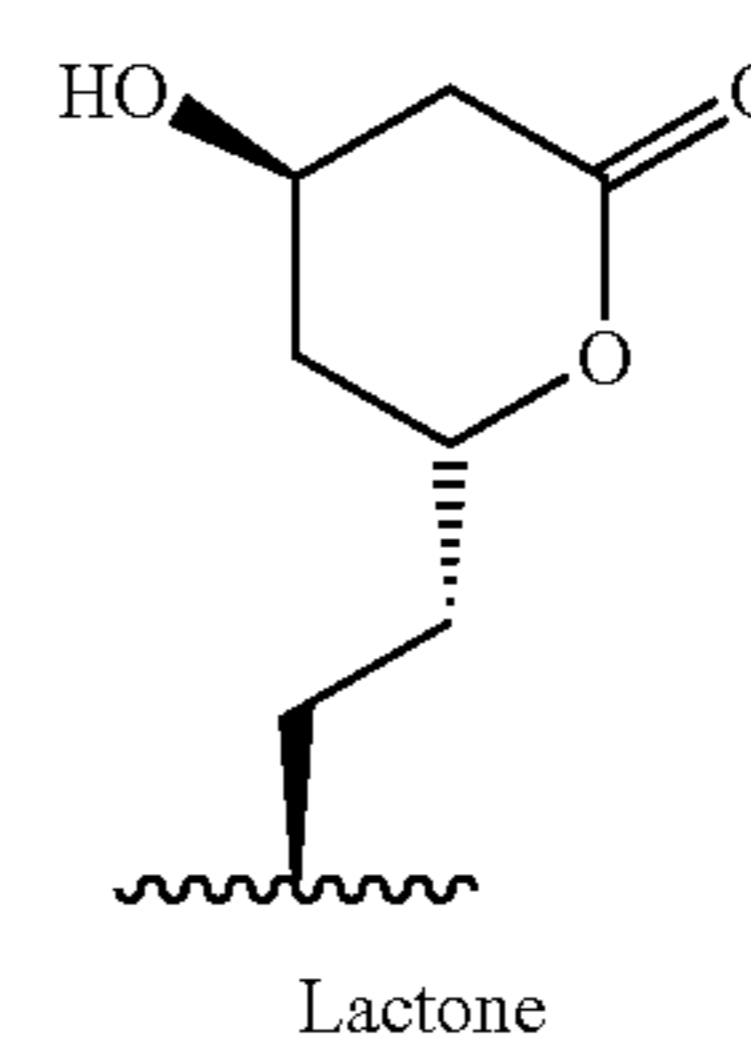
“An inhibitor of osteoclast proton ATPase” refers to an inhibitor of the proton ATPase, which is found on the apical membrane of the osteoclast, and has been reported to play a significant role in the bone resorption process. This proton pump represents an attractive target for the design of inhibitors of bone resorption which are potentially useful for the treatment and prevention of osteoporosis and related metabolic diseases. See C. Farina et al., “Selective inhibitors of the osteoclast vacuolar proton ATPase as novel bone anti-resorptive agents,” *DDT*, 4: 163–172 (1999), which is hereby incorporated by reference in its entirety.

“HMG-CoA reductase inhibitors” refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Pat. No. 4,231,938 at col. 6, and WO 84/02131 at pp. 30–33. The terms “HMG-CoA reductase inhibitor” and “inhibitor of HMG-CoA reductase” have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Pat. Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR® see U.S. Pat. Nos. 4,444,784, 4,820, 850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Pat. Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL® see U.S. Pat. Nos. 5,354, 772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896), atorvastatin (LIPITOR®; see U.S. Pat. Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL® see U.S.

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Pat. No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, “Cholesterol Lowering Drugs”, *Chemistry & Industry*, pp. 85–89 (5 Feb. 1996) and U.S. Pat. Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefore the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the lactone portion and its corresponding open-acid form is shown below as structures I and II.



In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term “HMG-CoA reductase inhibitor” as used herein. Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and most preferably simvastatin. Herein, the term “pharmaceutically-acceptable salts” with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not-limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate,

iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoate, tosylate, triiodide, and valerate.

Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

As used above, "integrin receptor antagonists" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_4$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. H. N. Lode and coworkers in PNAS USA 96: 1591–1596 (1999) have observed synergistic effects between an antiangiogenic α_v integrin antagonist and a tumor-specific antibody-cytokine (interleukin-2) fusion protein in the eradication of spontaneous tumor metastases. Their results suggested this combination as having potential for the treatment of cancer and metastatic tumor growth. $\alpha_v\beta_3$ integrin receptor antagonists inhibit bone resorption through a new mechanism distinct from that of all currently available drugs. Integrins are heterodimeric transmembrane adhesion receptors that mediate cell-cell and cell-matrix interactions. The α and β integrin subunits interact non-covalently and bind extracellular matrix ligands in a divalent cation-dependent manner. The most abundant integrin on osteoclasts is $\alpha_v\beta_3$ ($>10^7$ /osteoclast), which appears to play a rate-limiting role in cytoskeletal organization important for cell migration and polarization. The $\alpha_v\beta_3$ antagonizing effect is selected from inhibition of bone resorption, inhibition of restenosis, inhibition of macular degeneration, inhibition of arthritis, and inhibition of cancer and metastatic growth.

"An osteoblast anabolic agent" refers to agents that build bone, such as PTH. The intermittent administration of parathyroid hormone (PTH) or its amino-terminal fragments and analogues have been shown to prevent, arrest, partially reverse bone loss and stimulate bone formation in animals and humans. For a discussion refer to D. W. Dempster et al., "Anabolic actions of parathyroid hormone on bone," *Endocr Rev* 14: 690–709 (1993). Studies have demonstrated the clinical benefits of parathyroid hormone in stimulating bone formation and thereby increasing bone mass and strength. Results were reported by R M Neer et al., in *New Eng J Med* 344 1434–1441 (2001).

In addition, parathyroid hormone-related protein fragments or analogues, such as PTHrP-(1–36) have demonstrated potent anticalciuric effects [see M. A. Syed et al., "Parathyroid hormone-related protein-(1–36) stimulates renal tubular calcium reabsorption in normal human volunteers: implications for the pathogenesis of humoral hypercalcemia of malignancy," *JCEM* 86: 1525–1531 (2001)] and may also have potential as anabolic agents for treating osteoporosis.

Calcitonin is a 32 amino acid peptide produced primarily by the thyroid which is known to participate in calcium and

phosphorus metabolism. Calcitonin suppresses resorption of bone by inhibiting the activity of osteoclasts. Thus, calcitonin can allow osteoblasts to work more effectively and build bone.

"Vitamin D" includes, but is not limited to, vitamin D₃ (cholecalciferol) and vitamin D₂ (ergocalciferol), which are naturally occurring, biologically inactive precursors of the hydroxylated biologically active metabolites of vitamin D: 1 α -hydroxy vitamin D; 25-hydroxy vitamin D, and 1 α ,25-dihydroxy vitamin D. Vitamin D₂ and vitamin D₃ have the same biological efficacy in humans. When either vitamin D₂ or D₃ enters the circulation, it is hydroxylated by cytochrome P₄₅₀-vitamin D-25-hydroxylase to give 25-hydroxy vitamin D. The 25-hydroxy vitamin D metabolite is biologically inert and is further hydroxylated in the kidney by cytochrome P450-monooxygenase, 25 (OH) D-1 α -hydroxylase to give 1,25-dihydroxy vitamin D. When serum calcium decreases, there is an increase in the production of parathyroid hormone (PTH), which regulates calcium homeostasis and increases plasma calcium levels by increasing the conversion of 25-hydroxy vitamin D to 1,25-dihydroxy vitamin D.

1,25-dihydroxy vitamin D is thought to be responsible for the effects of vitamin D on calcium and bone metabolism. The 1,25-dihydroxy metabolite is the active hormone required to maintain calcium absorption and skeletal integrity. Calcium homeostasis is maintained by 1,25 dihydroxy vitamin D by inducing monocytic stem cells to differentiate into osteoclasts and by maintaining calcium in the normal range, which results in bone mineralization by the deposition of calcium hydroxyapatite onto the bone surface, see Holick, M F, "Vitamin D photobiology, metabolism, and clinical applications," in *Endocrinology*, 3rd ed., 990–1013 (1995), edited by DeGroot L et al. However, elevated levels of 1 α ,25-dihydroxy vitamin D₃ can result in an increase of calcium concentration in the blood and in the abnormal control of calcium concentration by bone metabolism, resulting in hypercalcemia. 1 α ,25-dihydroxy vitamin D₃ also indirectly regulates osteoclastic activity in bone metabolism and elevated levels may be expected to increase excessive bone resorption in osteoporosis.

"Synthetic vitamin D analogues" includes non-naturally occurring compounds that act like vitamin D.

Selective Serotonin Reuptake Inhibitors act by increasing the amount of serotonin in the brain. SSRIs have been used successfully for a decade in the United States to treat depression. Non-limiting examples of SSRIs include fluoxetine, paroxetine, sertraline, citalopram, and fluvoxamine. SSRIs are also being used to treat disorders related to estrogen functioning, such as premenstrual syndrome and premenstrual dysmorphic disorder. See Sundstrom-Poromaa I, Bixo M, Bjorn I, Nordh O., "Compliance to antidepressant drug therapy for treatment of premenstrual syndrome," *J Psychosom Obstet Gynaecol*, 2000 December; 21(4):205–11.

As used herein the term "aromatase inhibitor" includes compounds capable of inhibiting aromatase, for example commercially available inhibitors such as: aminoglutemide (CYTANDREN®), Anastrozole (ARIMIDEX®), Letrozole (FEMARA®), Formestane (LENATRON®), Exemestane (AROMASIN®), Atamestane (1-methylandrosta-1,4-diene-3,17-dione), Fadrozole (4-(5,6,7,8-Tetrahydroimidazo[1,5-a]pyridin-5-yl)-benzotrile, monohydrochloride), Finrozole (4-(3-(4-Fluorophenyl)-2-hydroxy-1-(1H-1,2,4-triazol-1-yl)-propyl)-benzotrile), Vorozole (6-[(4-chlorophenyl)-1H-1,2,4-triazol-1-ylmethyl]-1-methyl-1H-benzotriazole),

YM-511 (4-[N-(4-bromobenzyl)-N-(4-cyanophenyl) amino]-4H-1,2,4-triazole) and the like.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a bisphosphonate, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents. The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985, which is incorporated by reference herein in its entirety. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

The present invention also encompasses a pharmaceutical composition useful in the treatment of the diseases mentioned herein, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's bloodstream by local bolus injection.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment. Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10

mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds of the present invention can be used in combination with other agents useful for treating estrogen-mediated conditions. The individual components of such combinations can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating cathepsin-mediated conditions includes in principle any combination with any pharmaceutical composition useful for treating disorders related to estrogen functioning.

The scope of the invention therefore encompasses the use of the instantly claimed compounds in combination with a second agent selected from: an organic bisphosphonate; a cathepsin K inhibitor; an estrogen; an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent; calcitonin; Vitamin D; a synthetic Vitamin D analogue; a selective serotonin reuptake inhibitor; an aromatase inhibitor; and the pharmaceutically acceptable salts and mixtures thereof.

These and other aspects of the invention will be apparent from the teachings contained herein.

DEFINITIONS

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The terms "treating" or "treatment" of a disease as used herein includes: preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease; inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms; or relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

The term "bone resorption" as used herein, refers to the process by which osteoclasts degrade bone.

The term "alkyl" shall mean a substituting univalent group derived by conceptual removal of one hydrogen atom from a straight or branched-chain acyclic saturated hydro-

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carbon (i.e., $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, etc.).

The term "alkenyl" shall mean a substituting univalent group derived by conceptual removal of one hydrogen atom from a straight or branched-chain acyclic unsaturated hydrocarbon (i.e., $-\text{CH}=\text{CH}_2$, $-\text{CH}=\text{CHCH}_3$, $-\text{C}=\text{C}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}=\text{CH}_2$, etc.).

The term "alkynyl" shall mean a substituting univalent group derived by conceptual removal of one hydrogen atom from a straight or branched-chain acyclic unsaturated hydrocarbon containing a carbon-carbon triple bond (i.e., $-\text{C}-\text{CH}$, $-\text{C}\equiv\text{CCH}_3$, $-\text{C}\equiv\text{CCH}(\text{CH}_3)_2$, $-\text{CH}_2\text{C}\equiv\text{CH}$, etc.).

The term "alkylidene" shall mean a substituting bivalent group derived from a straight or branched-chain acyclic saturated hydrocarbon by conceptual removal of two hydrogen atoms from the same carbon atom (i.e., $=\text{CH}_2$, $=\text{CHCH}_3$, $=\text{C}(\text{CH}_3)_2$, etc.).

The term "cycloalkyl" shall mean a substituting univalent group derived by conceptual removal of one hydrogen atom from a saturated monocyclic hydrocarbon (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl).

The term "aryl" as used herein refers to a substituting univalent group derived by conceptual removal of one hydrogen atom from a monocyclic or bicyclic aromatic hydrocarbon. Examples of aryl groups are phenyl, indenyl, and naphthyl.

The term "heteroaryl" as used herein refers to a substituting univalent group derived by the conceptual removal of one hydrogen atom from a monocyclic or bicyclic aromatic ring system containing 1, 2, 3, or 4 heteroatoms selected from N, O, or S. Examples of heteroaryl groups include, but are not limited to, pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, pyrimidinyl, pyrazinyl, benzimidazolyl, indolyl, and purinyl. Heteraryl substituents can be attached at a carbon atom or through the heteroatom.

The term "halo" shall include iodo, bromo, chloro and fluoro.

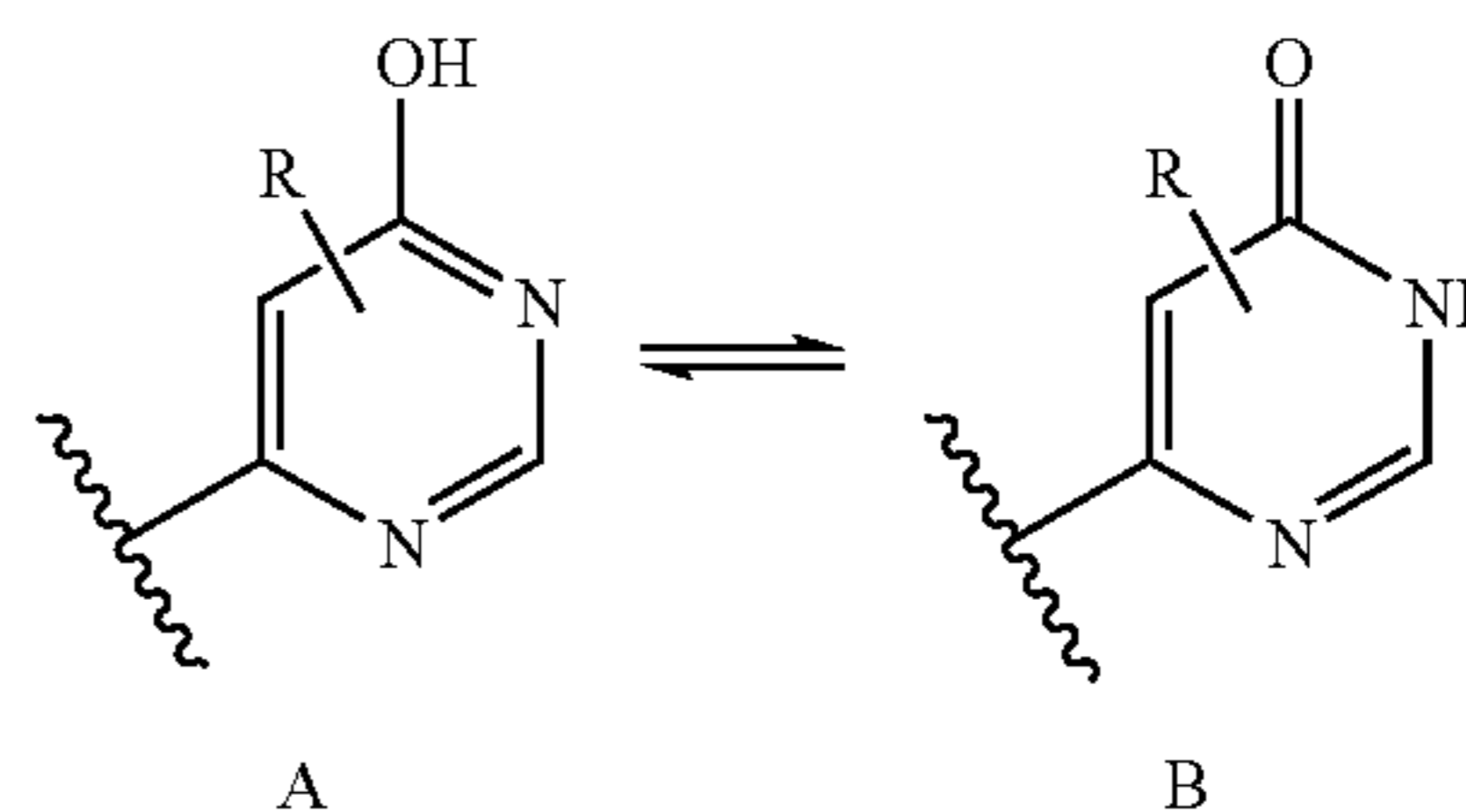
The term "substituted" shall be deemed to include multiple degrees of substitution by a named substituent. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

The present invention also includes protected derivatives of compounds disclosed herein. For example, when compounds of the present invention contain groups such as hydroxyl or carbonyl, these groups can be protected with a suitable protecting group. A comprehensive list of suitable protective groups can be found in T. W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981, the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of the present invention can be prepared by methods well known in the art.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in E. L. Eliel and S. H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119–1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention. In addition, the compounds dis-

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closed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted. For example, any claim to compound A below is understood to include tautomeric structure B, and vice versa, as well as mixtures thereof.



When any variable (e.g. R^1 , R^2 , R^3 etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms. If the ring system is polycyclic, it is intended that the bond be attached to any of the suitable carbon atoms on the proximal ring only.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one substituent" and in such cases the preferred embodiment will have from zero to three substituents.

In choosing compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R^1 , R^2 and R^3 are to be chosen in conformity with well-known principles of chemical structure connectivity.

Representative compounds of the present invention typically display submicromolar affinity for alpha and/or beta estrogen receptors, and preferably agonize the beta estrogen receptor. Compounds of this invention are therefore useful in treating mammals suffering from disorders related to estrogen functioning.

The compounds of the present invention are available in racemic form or as individual enantiomers. For convenience, some structures are graphically represented as a single enantiomer but, unless otherwise indicated, is meant to include both racemic and enantiomerically pure forms. Where cis and trans stereochemistry is indicated for a compound of the present invention, it should be noted that the stereochemistry should be construed as relative, unless indicated otherwise. For example, a (+) or (−) designation should be construed to represent the indicated compound with the absolute stereochemistry as shown.

Racemic mixtures can be separated into their individual enantiomers by any of a number of conventional methods. These include, but are not limited to, chiral chromatography,

derivatization with a chiral auxillary followed by separation by chromatography or crystallization, and fractional crystallization of diastereomeric salts. Deracemization procedures may also be employed, such as enantiomeric protonation of a pro-chiral intermediate anion, and the like.

The compounds of the present invention can be used in combination with other agents useful for treating estrogen-mediated conditions. The individual components of such combinations can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating estrogen-mediated conditions includes in principle any combination with any pharmaceutical composition useful for treating disorders related to estrogen functioning.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician, veterinarian or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed inorganic or organic acids. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like. The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977, 66:1-19, hereby incorporated by reference. The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

In the schemes and examples below, various reagent symbols and abbreviations have the following meanings:

AlCl₃: Aluminum chloride
 BBr₃: Boron Tribromide
 BrCH₂CH₂F: 1-Bromo-2-fluoroethane
 BrCH₂CH₂OBn: 1-Bromo-2-benzyloxyethane
 5 CH₂Cl₂: Dichloromethane
 DBN: 1,5-diazabicyclo[4.3.0]non-5-ene
 DMAC: N,N-Dimethylacetamide
 DMF: Dimethylformamide
 EtOH: Ethanol
 10 Et₃N: Triethylamine
 EtSH: ethanethiol
 EVK: Ethyl vinyl ketone
 HCl: Hydrochloric acid
 HOAc: Acetic Acid
 15 K₂CO₃: Potassium carbonate
 KI: Potassium iodide
 KN(TMS)₂: Potassium bis(trimethylsilyl)amide
 LiCl: Lithium chloride
 LDA: Lithium Dimethylamide
 20 LiN(TMS)₂: Lithium bis(trimethylsilyl)amide
 Me₂CO₃: Methyl carbonate
 MeCN: Methyl cyanide
 MeOH: Methanol
 MsCl: Mesyl chloride
 25 MVK: Methyl vinyl ketone
 NaH: Sodium hydride
 NaI: Sodium iodide
 NaOH: Sodium hydroxide
 NaOMe: Sodium methylate
 30 NCCO₂Et: Ethyl cyanofornate
 NBS: N-Bromo Succinimide
 NCS: N-Chloro Succinimide
 PdCl₂(PPh₃)₂: Bis(triphenylphosphine)palladium(II) chloride
 35 Pd(PPh₃)₄: Tetrakis(triphenylphosphine)palladium(0)
 PhB(OH)₂: Phenyl borohydride
 PhCH₃: Methyl phenyl
 PhH: Phenyl hydride
 40 PhMe: Methyl phenyl
 SnMe₄: Tetramethyltin
 THF: Tetrahydrofuran

The novel compounds of the present invention can be prepared according to the procedure of the following schemes and examples, using appropriate materials and are further exemplified by the following specific examples. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless otherwise noted.

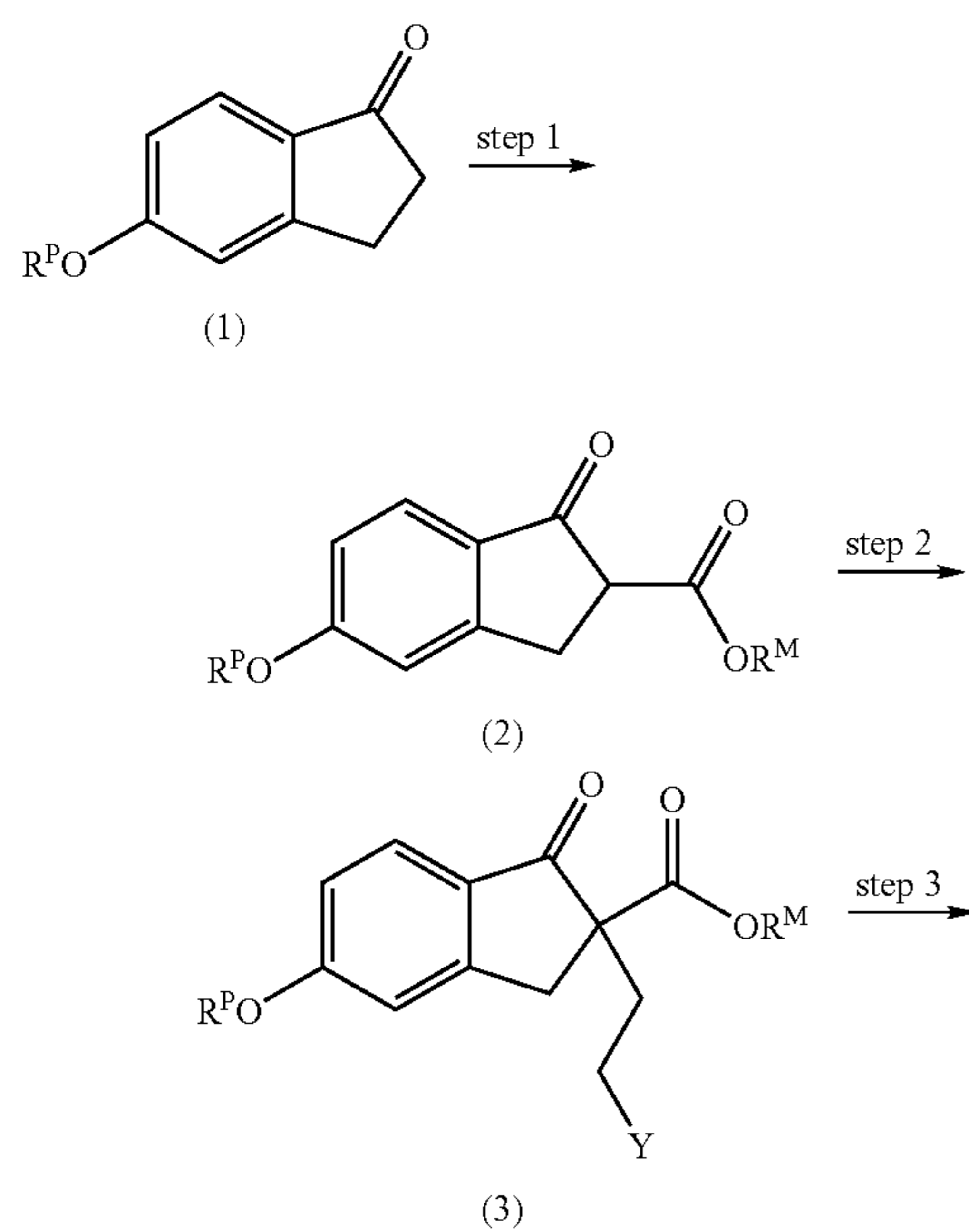
The compounds of the present invention are prepared according to the general methods outlined in Schemes I-V. In these schemes, R^I represents R³ or a precursor thereof; R^{II} represents R¹ or a precursor thereof; R^{III} represents R⁶ or a precursor thereof; R^{IVa} and R^{IVb} represent non-hydrogen values of R⁴ and/or R⁵; R^V represents OR^a and NR^aR^a; R^{VI} represents hydrogen or a C₁₋₅ alkyl group; R^P represents R² or a removable protecting group for a phenolic hydroxyl such as methyl, methoxymethyl or benzyl; R^M represents a carboxyl esterifying group such as methyl, ethyl, allyl or benzyl; and Y represents a displaceable leaving group such as fluoro, chloro, bromo, iodo; methanesulfonyloxy, p-tolu-

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enesulfonyloxy, trifluoromethylsulfonyloxy a precursor thereof such as benzyloxy or acetoxy.

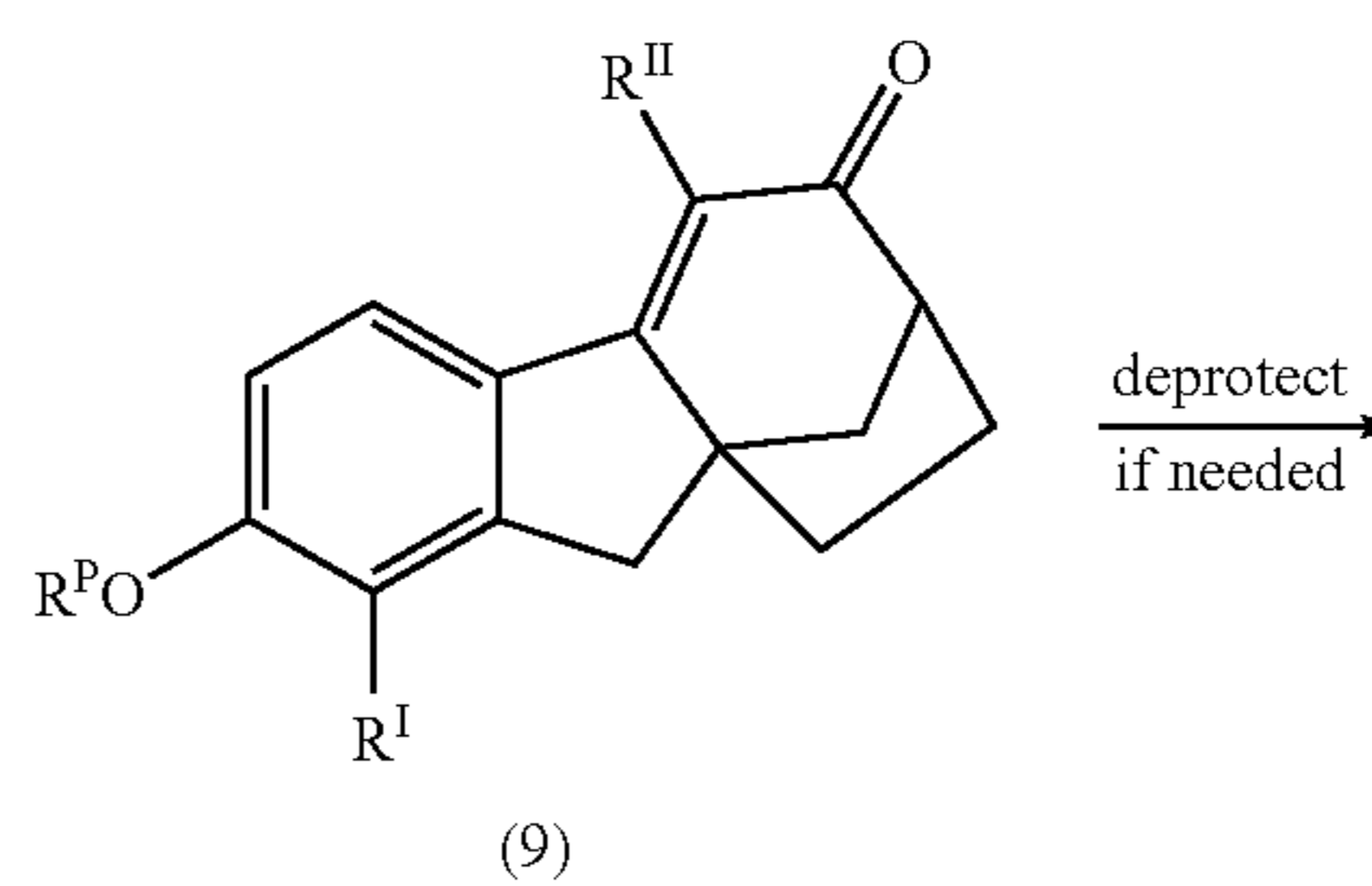
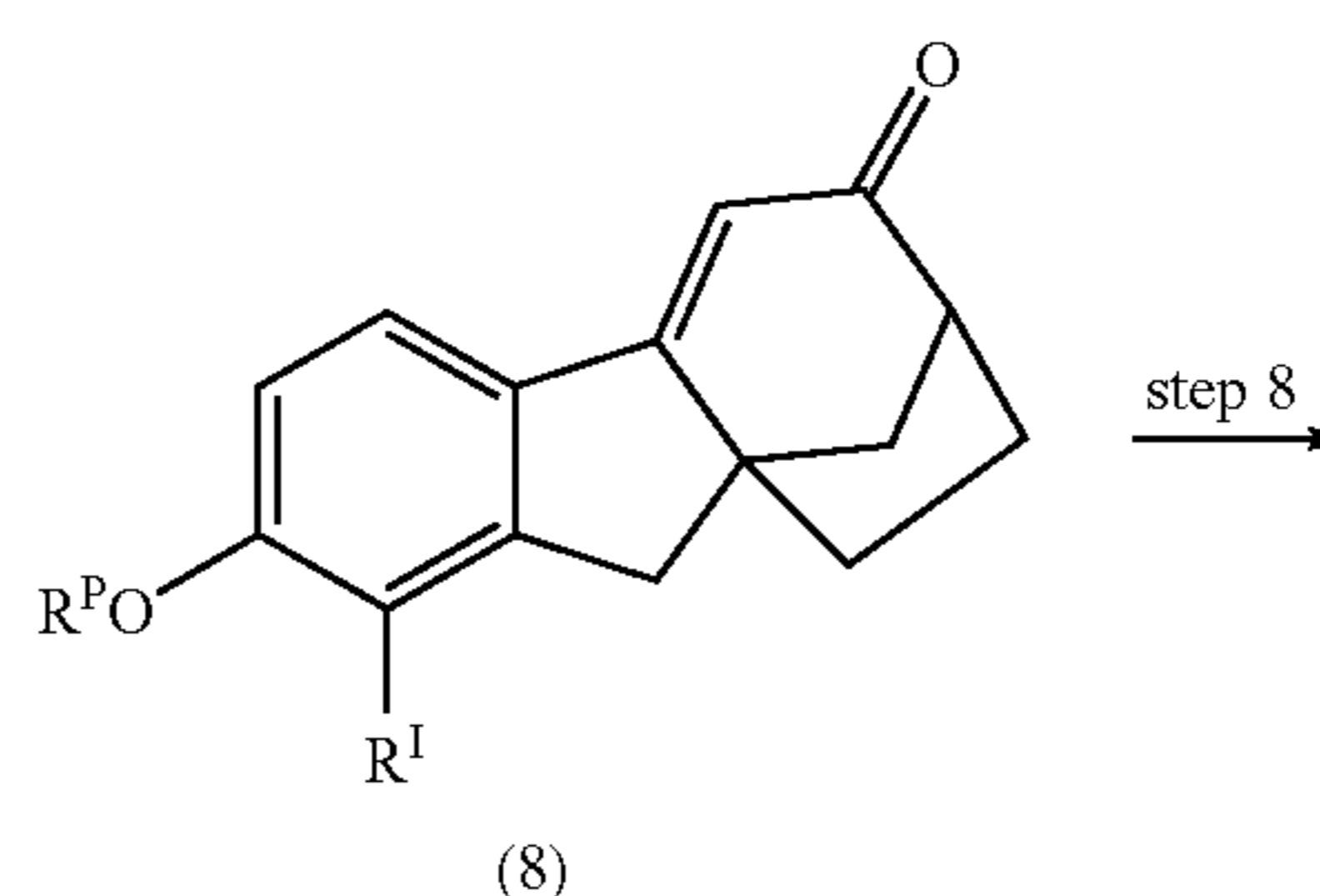
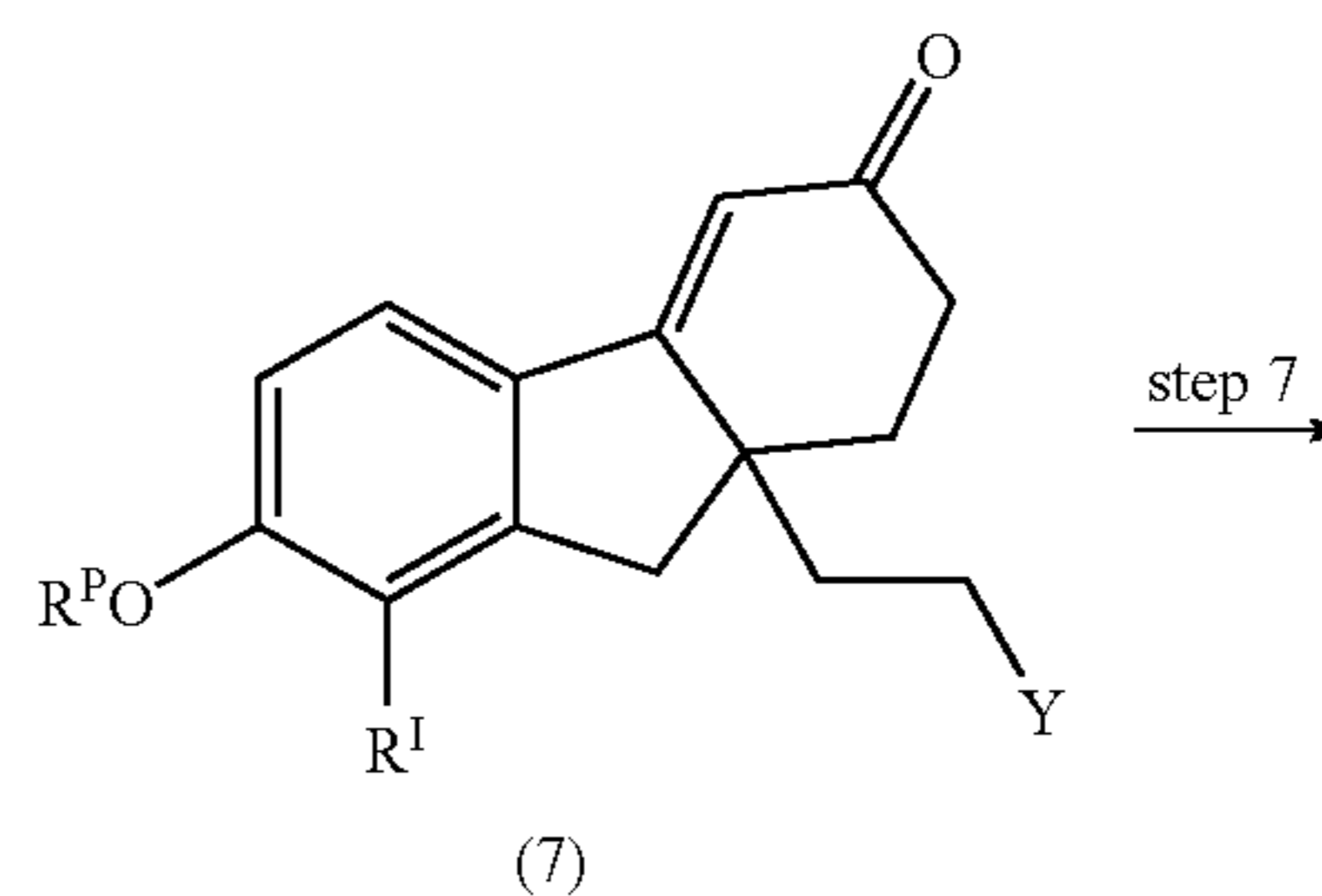
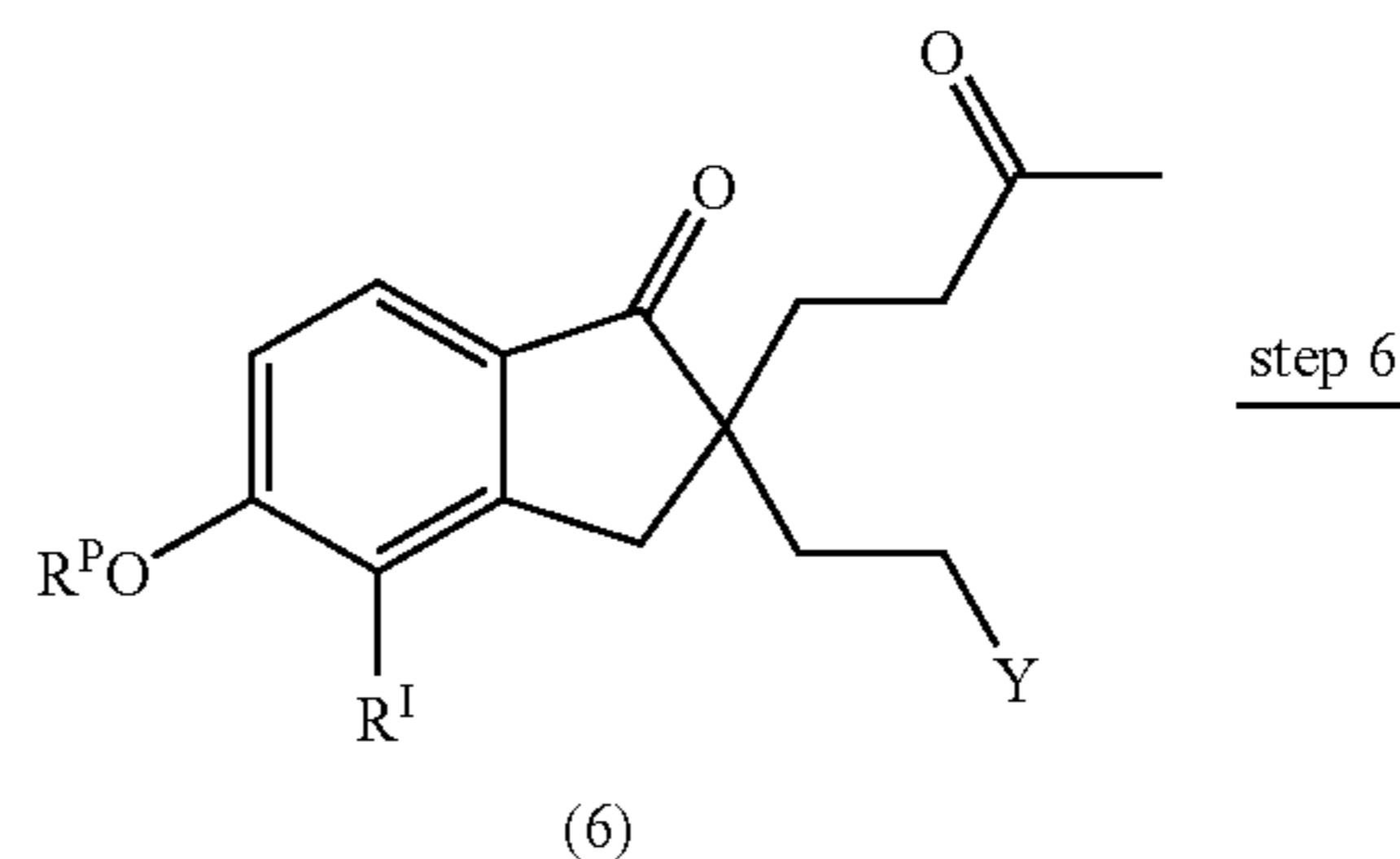
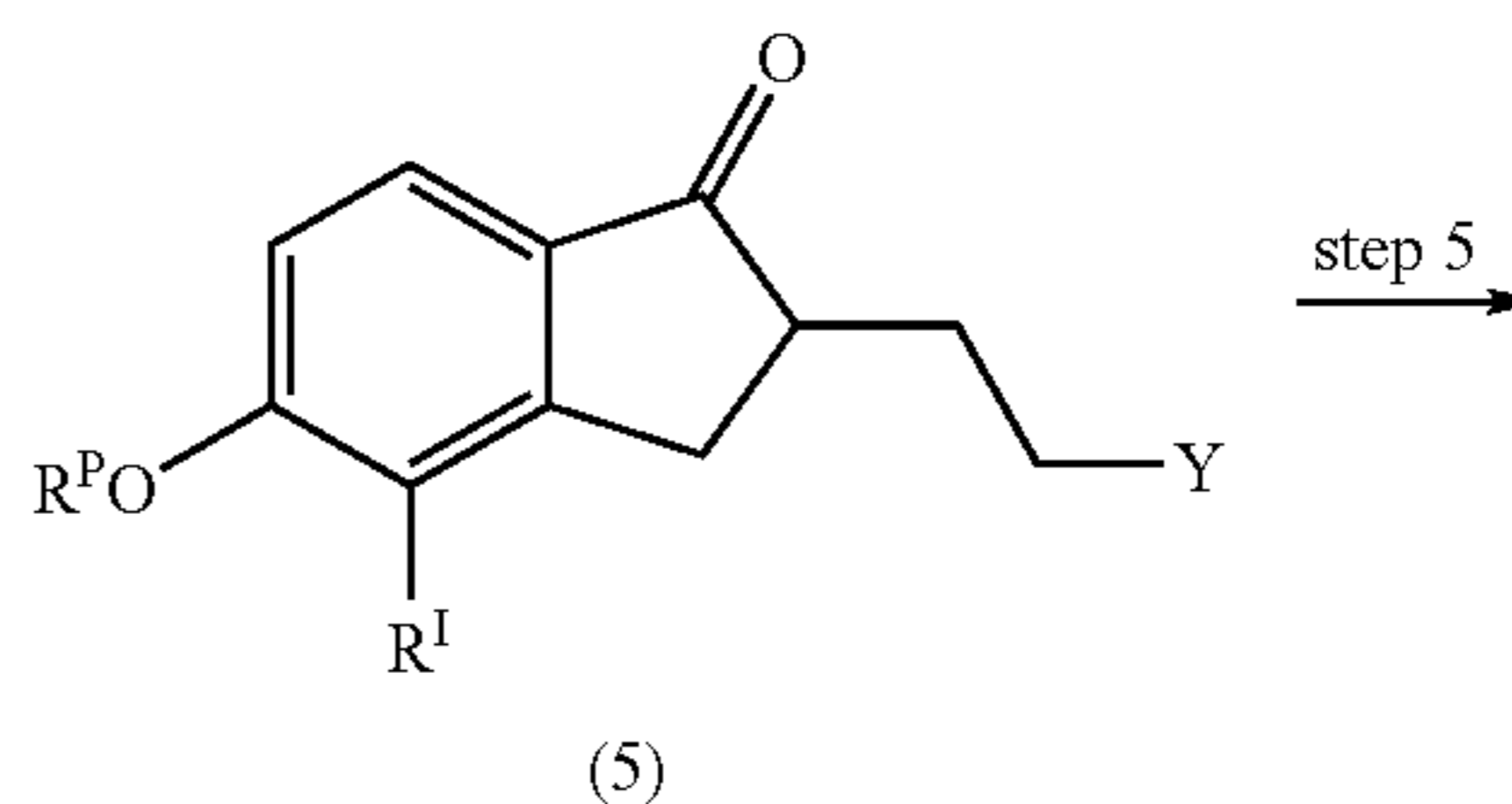
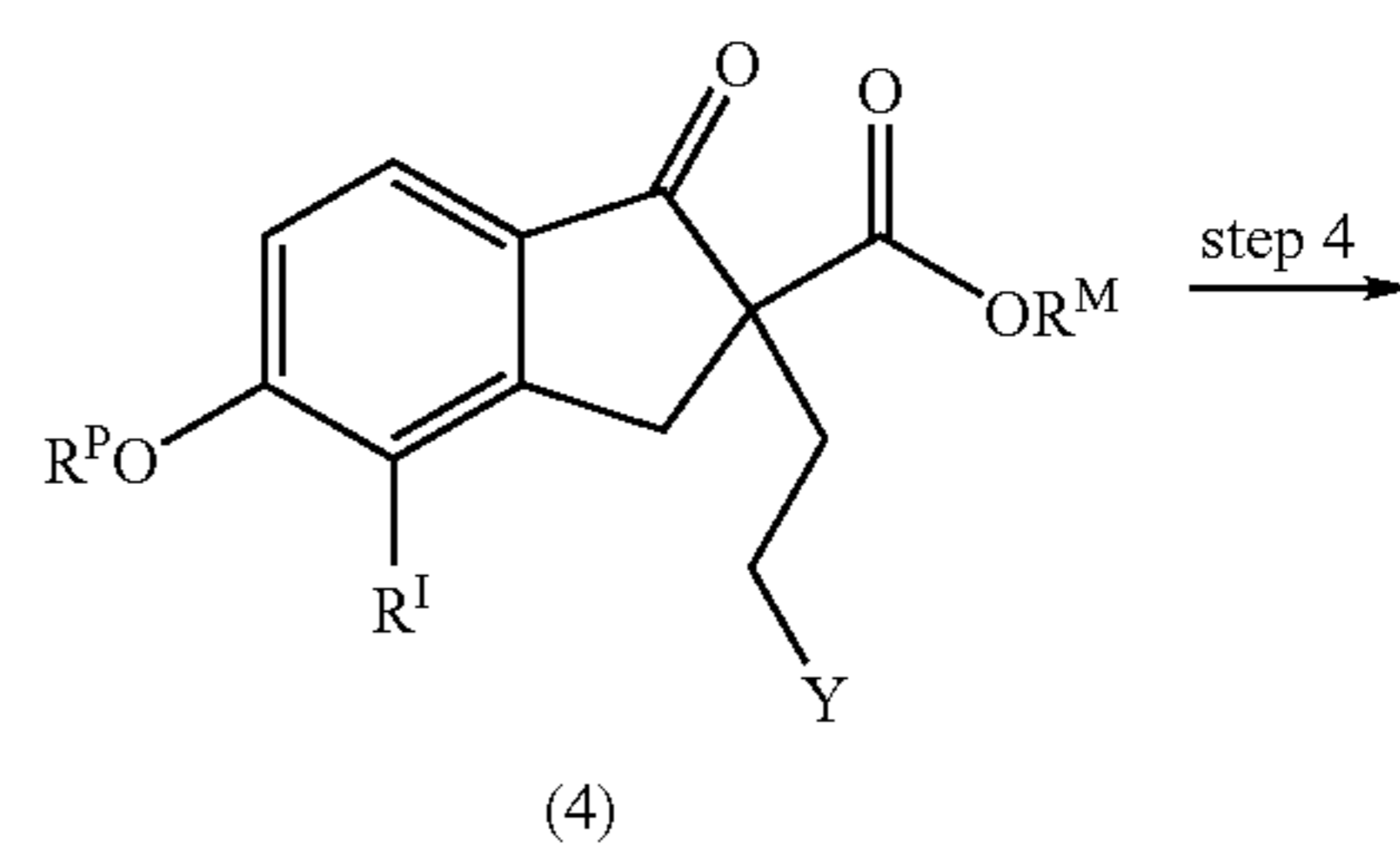
The starting materials for the synthesis of Scheme 1 are 5-alkoxy-1-indanones (1), which are either known compounds or can be prepared by conventional methods known in the art. In step 1 of Scheme I, a 5-alkoxy-1-indanone (1) is reacted with a carboxylating reagent such as ethyl cyanofornate or ethyl chloroformate in the presence of base to provide the beta-ketoester (2). In step 2, the beta-ketoester (2) is then reacted with an alkylating agent $Z-CH_2CH_2-Y$, where Z represents a displaceable leaving group, in the presence of a base to give intermediate (3). In the case where Y also represents a displaceable leaving group, the relative reactivities of the two groups are appropriately chosen so that Z is the more easily displaced group. In step 3 the R^I substituent is introduced at the 4-position of the indanone by an electrophilic aromatic substitution reaction employing a suitable electrophilic reagent. For introduction of certain R^I groups, this initial electrophilic aromatic substitution reaction may be followed by a transition metal catalyzed cross-coupling reaction. Alternatively, step 3 can be deferred and carried-out after step 4 or after step 6. In step 4, the carboxyl group of intermediate (4) is removed by hydrolysis or other cleavage of the ester followed by decarboxylation to give (5). In step 5, the 2-substituted indanone (5) reacts with methyl vinyl ketone in the presence of base to give the diketone (6). The diketone is then cyclized (step 6) under basic or acidic conditions to provide the tetrahydrofluorenone product (7). In step 7, the ethylidene bridge is formed by an internal alkylation reaction in the presence of a base and/or with heating. Conversion of Y to a reactive leaving group may be required prior to or in conjunction with this step. In step 8, the R^{II} substituent is introduced on the enone double-bond. Generally this is accomplished by a halogenation reaction which may then be followed by a substitution reaction to introduce various other substituents, for example alkyl and aryl groups. Depending on the selected R^I group, a final deprotection step may be needed to generate the final compound (10).

SCHEME 1



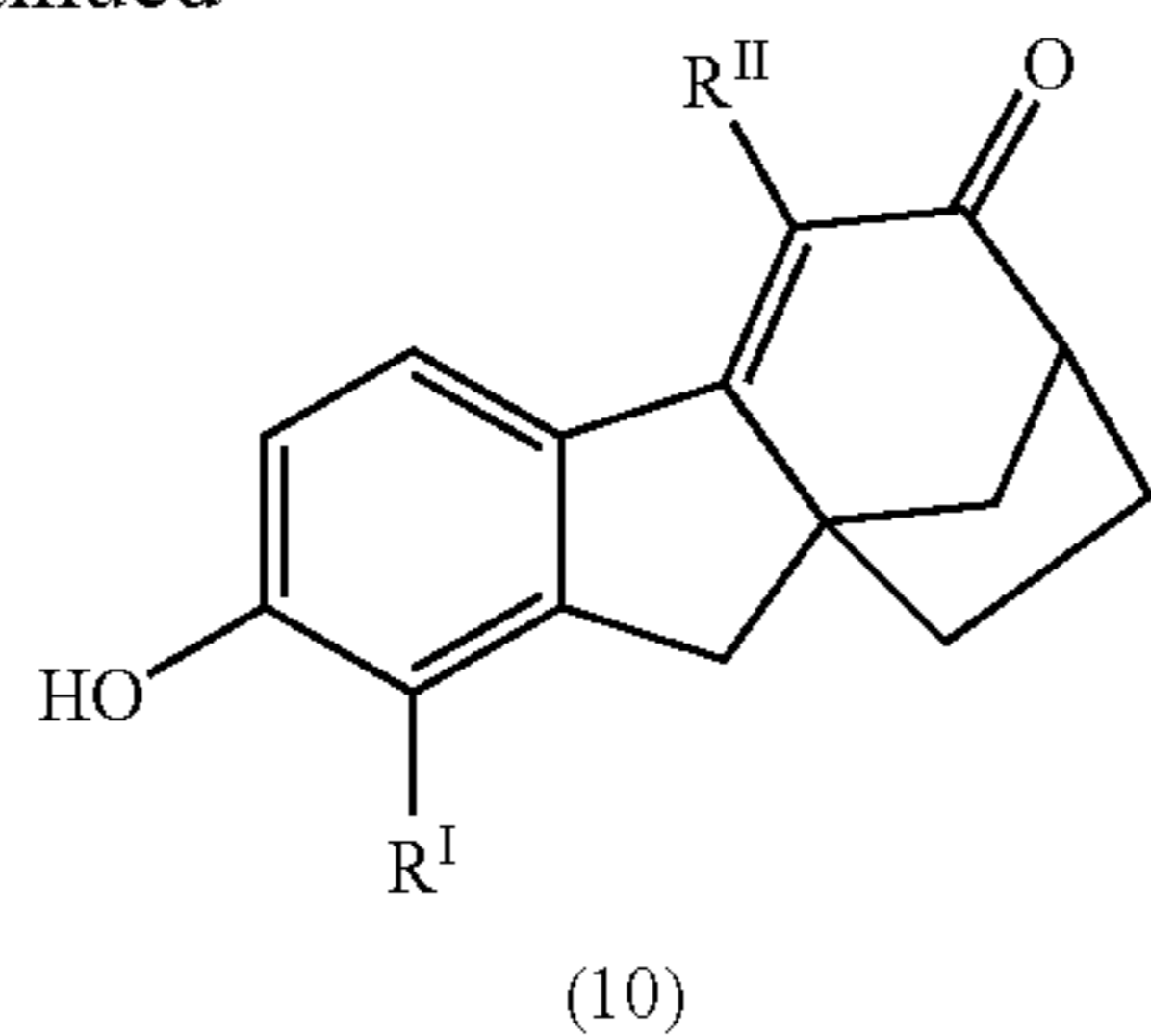
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Representative reagents and reaction conditions indicated in Scheme I as steps 1–8 are as follows:

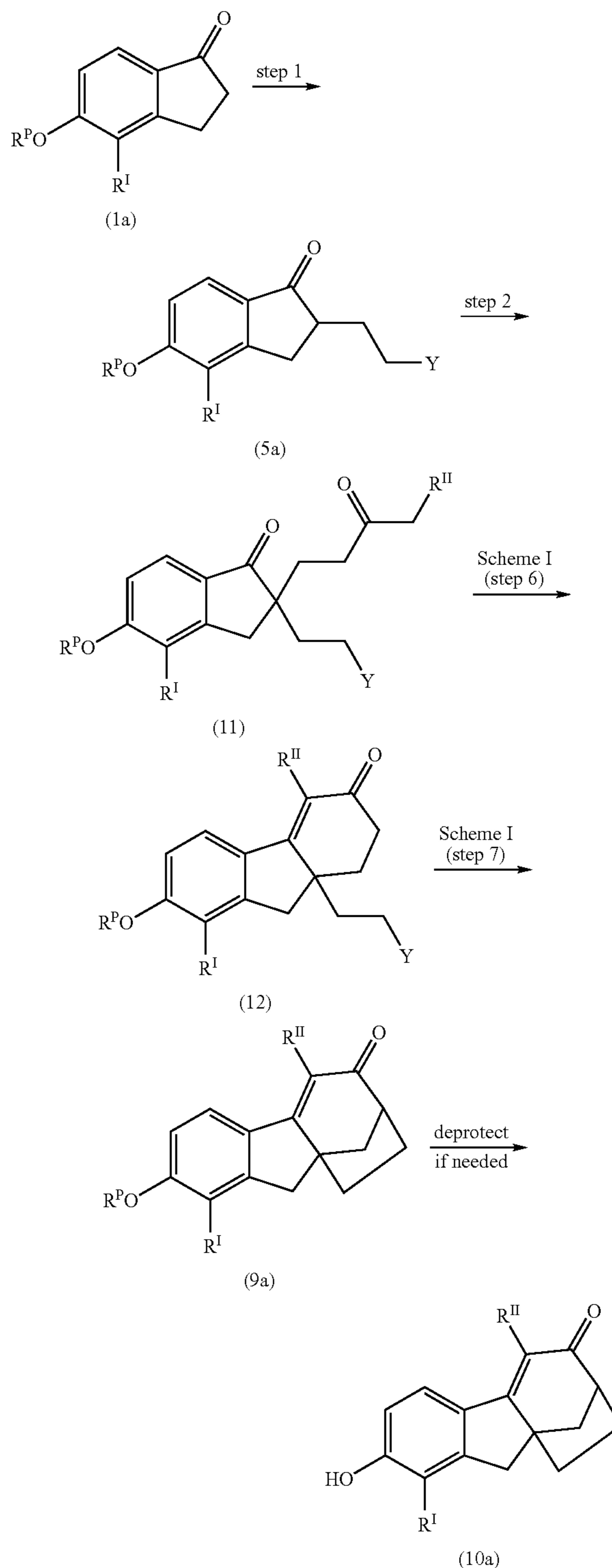
Step 1	i) LiN(TMS) ₂ , THF, -78 to 40° C. ii) NCCO ₂ Et, -78° C. to rt	R ^M = Et R ^M = Me
Step 2	BrCH ₂ CH ₂ F, K ₂ CO ₃ , KI, DMAC, 65° C. BrCH ₂ CH ₂ OBn, K ₂ CO ₃ , KI, DMAC, 60–100° C.	Y = F Y = OBn
Step 3	NCS, DMF, 50° C. NBS, DMF, rt to 50° C. Accufluor™ NFTh, MeCN, 50 to 80° C. i) NBS, DMF, rt to 50° C.	R ^I = Cl R ^I = Br R ^I = F R ^I = Me
Step 4	ii) SnMe ₄ , PdCl ₂ (PPh ₃) ₂ , DMF, rt to 120° C. NaOH, H ₂ O, MeOH, THF 0 to 40° C. or 6N HCl, HOAc, 90–100° C.,	
Step 5	MVK, NaOMe, MeOH, rt to 60° C. or MVK, DBN, THF, rt to 60° C.	
Step 6	pyrrolidine, HOAc, THF or PhMe, 60–85° C. or NaOH, H ₂ O, MeOH or EtOH, rt to 85° C. or 6N HCl, HOAc, 90–100° C.	
Step 7	LiCl, DMF, 150° C. i) BBr ₃ , CH ₂ Cl ₂ , -78° C. ii) KN(TMS) ₂ , THF, -78° C. to 0° C. pyridine-HCl, 190° C.	Y = F Y = F Y = OBn Y = OAc
Step 8	i) NaOMe, MeOH ii) MsCl, Et ₃ N, CH ₂ Cl ₂ iii) LDA, THF, -78° C. to rt NCS, DMF, 50° C. NBS, DMF, rt to 50° C. i) NBS, DMF, rt to 50° C. ii) PhB(OH) ₂ , Cs ₂ CO ₃ , PdCl ₂ (PPh ₃) ₂ , DMF, rt to 100° C.	R ^{II} = Cl R ^{II} = Br R ^{II} = Ph

Scheme II illustrates a variation of the synthesis shown in Scheme I. In this variation, the starting indanone (1a) is already substituted with the R^I substituent at position 4. Indanones (1a) are either known compounds or can be prepared by conventional methods known in the art. In step 1 of Scheme II, the indanone (1a) is substituted at the 2-position with the moiety —CH₂CH₂—Y. This can be accomplished by a reductive alkylation reaction wherein (1a) is reacted with a substituted aldehyde Y—CH₂CHO under basic conditions followed by hydrogenation of the resulting alkylidene intermediate. In this instance Y is most appropriately a precursor group which can be converted to a displaceable leaving group. Alternatively, introduction of the moiety —CH₂CH₂—Y can be accomplished by reacting indanone (1a) with an alkylating agent Z-CH₂CH₂—Y, where Z represents a displaceable leaving group, in the presence of a base to give intermediate (2). In the case where Y also represents a displaceable leaving group, the relative reactivities of the two groups are appropriately chosen so that Z is the more easily displaced group. Step 2 in Scheme II is analogous to step 5 of Scheme I, but employs the

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substituted vinyl ketone CH₂CH₂COCH₂R^{II} in place of methyl vinyl ketone. Diketone (11) is then converted to (10a) by the procedures previously described in Scheme I except that a separate step to introduce the R^{II} substituent is not required since it is incorporated in step 2 of Scheme II.

SCHEME II



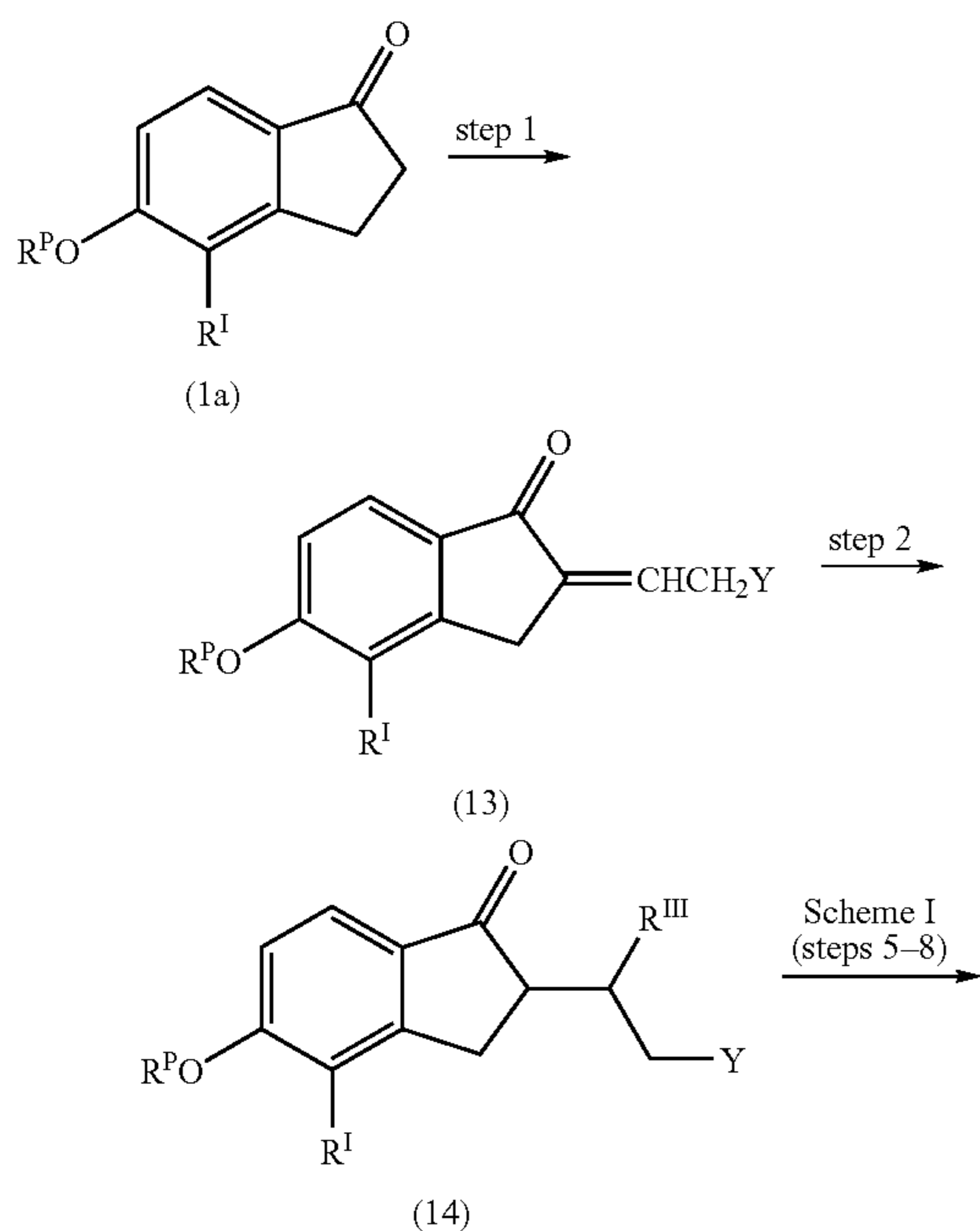
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Representative reagents and reaction conditions indicated in Scheme II as steps 1–2 are as follows:

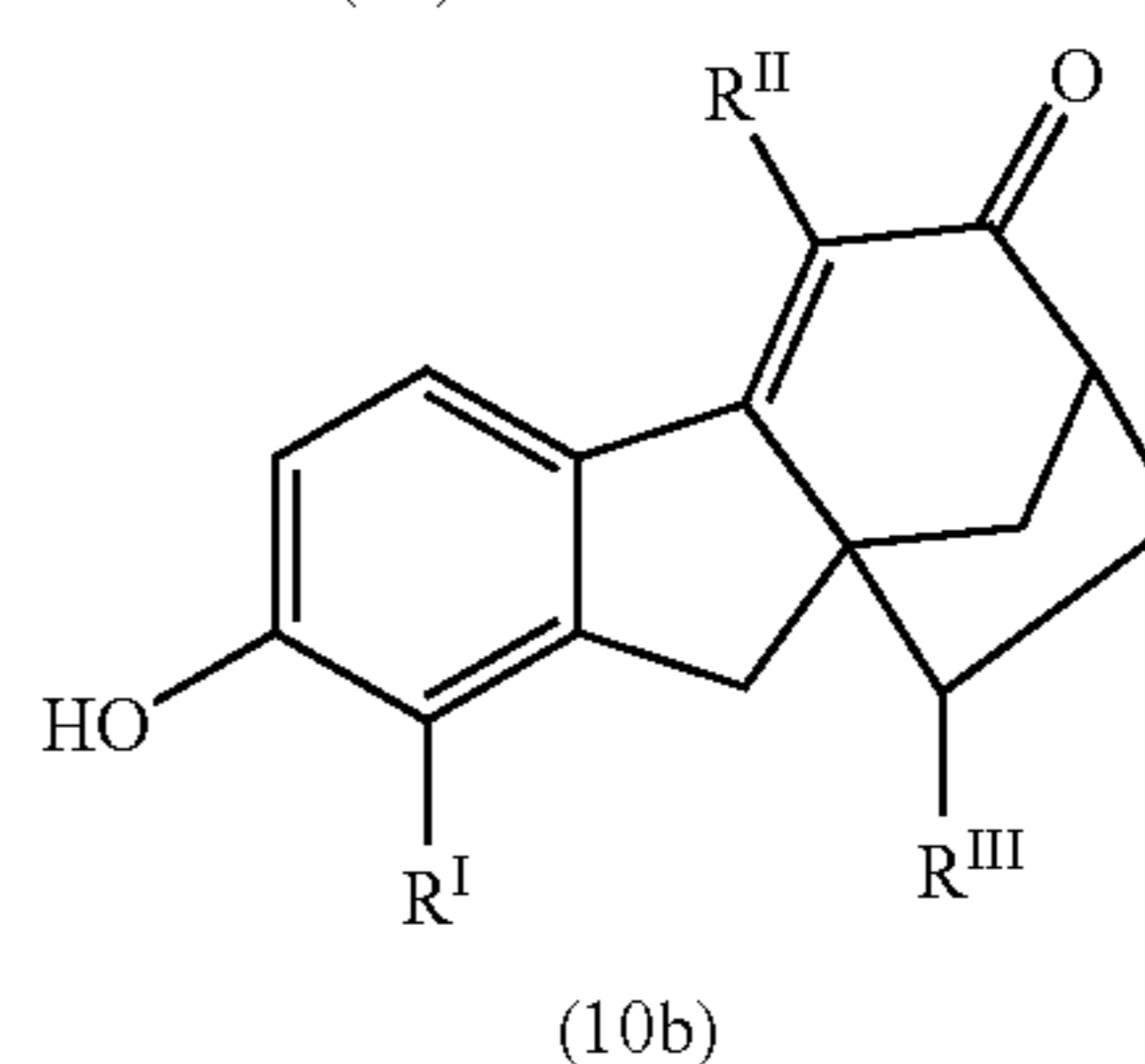
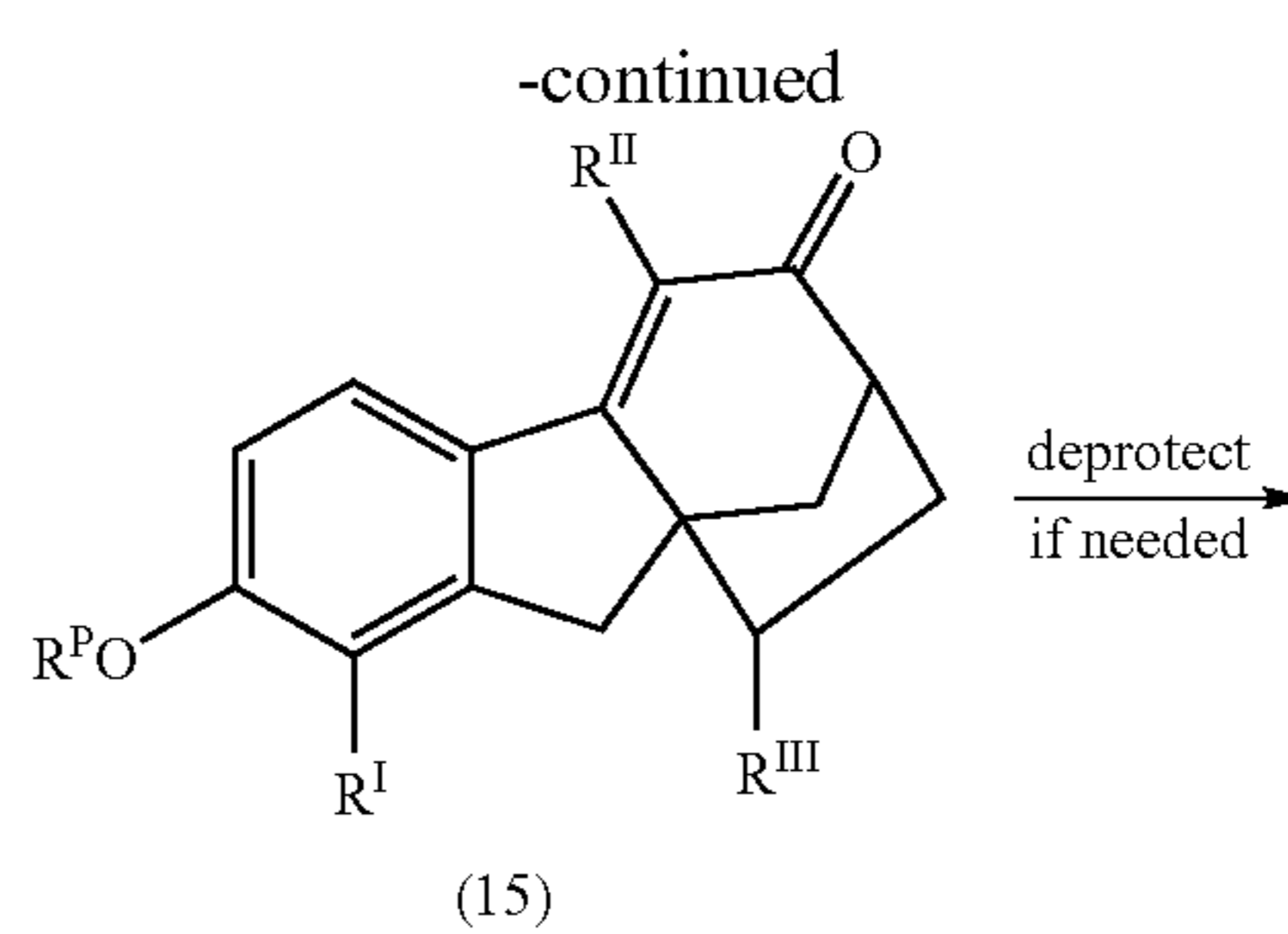
Step 1	BnOCH ₂ CHO, NaOMe, MeOH, H ₂ , Pd/C (HOCH ₂ CHO) ₂ , NaOMe, MeOH, H ₂ , Pd/C	Y = OBn Y = OH	5
Step 2	CH ₂ =CHC(O)CH ₂ R ^{II} , NaOMe, MeOH, rt to 60° C. or CH ₂ =CHC(O)CH ₂ R ^{II} , DBN, THF, rt to 60° C.		10

Scheme III illustrates a variation of the synthesis shown in Scheme II which allows for introduction of the R^{III} substituent. Step 1 of Scheme III is similar to step 1 of Scheme II except that the reduction step is omitted and the alkylidene intermediate (13) is obtained. Introduction of the R^{III} substituent is accomplished in step 2 by reaction of (13) with an appropriate organometallic species to give (14) via a 1,4-conjugate addition reaction. Indanone (14) is then converted to (10b) by the procedures previously described in Scheme I.

SCHEME III



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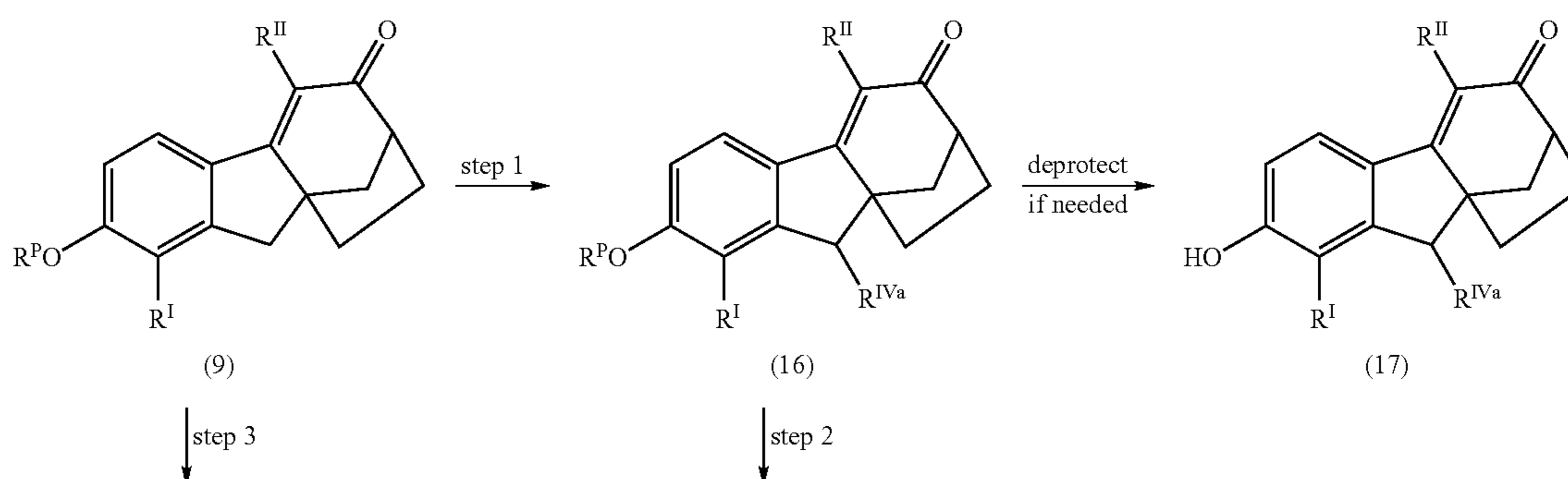


Representative reagents and reaction conditions indicated in Scheme III as steps 1–2 are as follows:

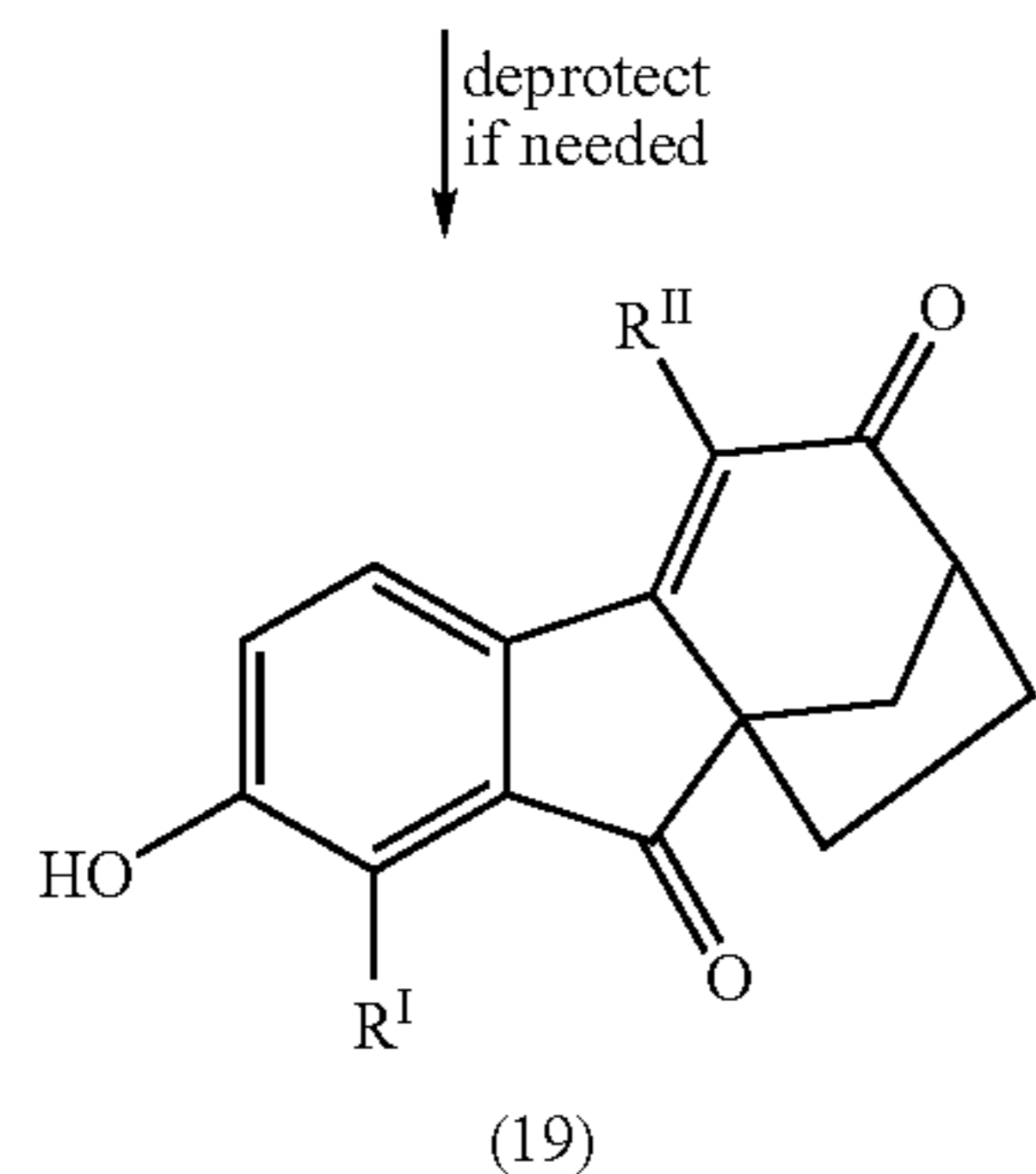
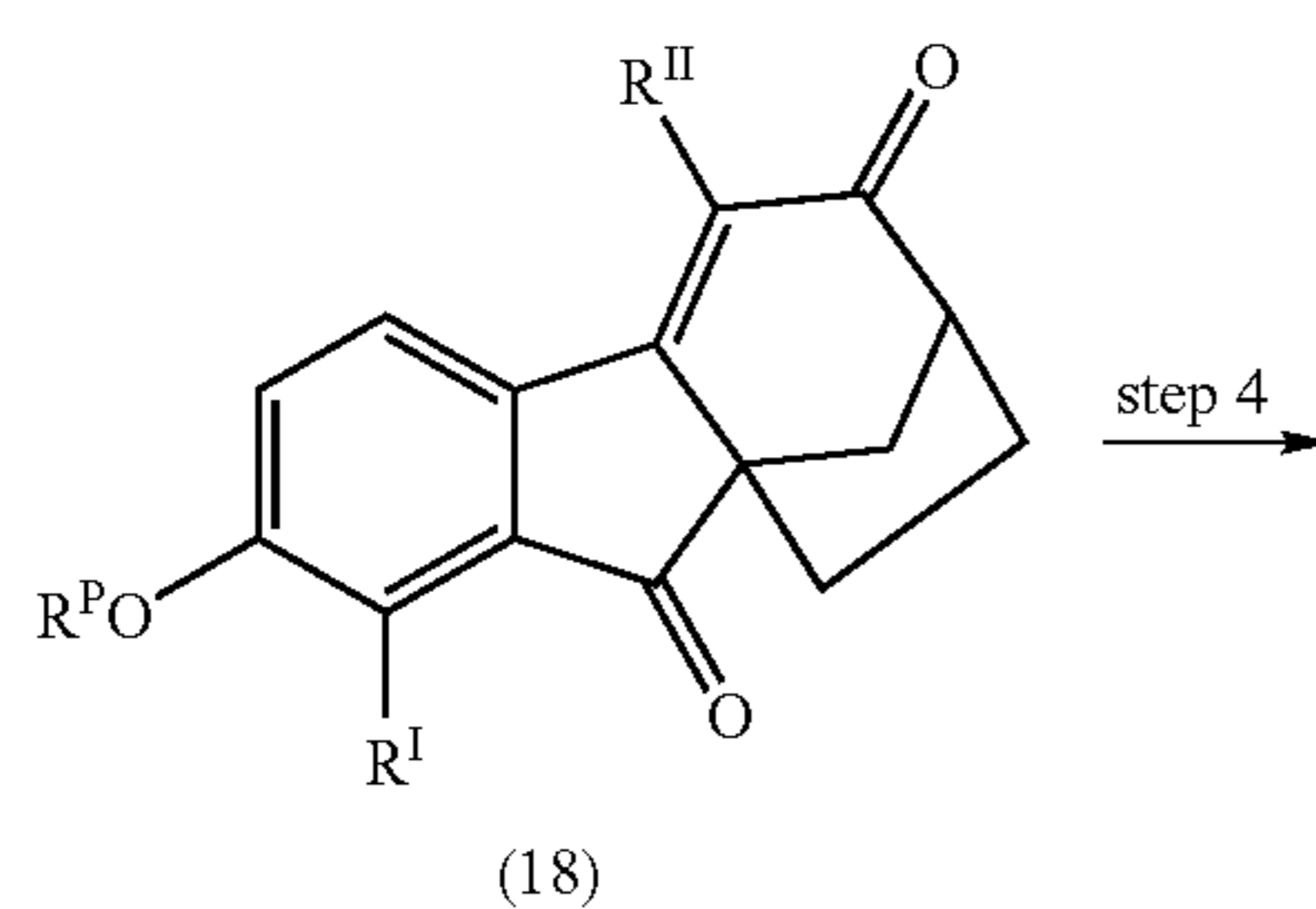
Step 1	BnOCH ₂ CHO, KOH, MeOH or i) LiN(TMS) ₂ , THF, -78° C. to -40° C. ii) BnOCH ₂ CHO, -78° C. to rt iii) MsCl, Et ₃ N, CH ₂ Cl ₂	Y = OBn	25
Step 2	R ^{III} MgBr, CuBr.SMe ₂ , THF -78° C. to rt or R ^{III} ₂ CuLi, THF -78° C. to rt		30

Final compounds bearing substituents at the 10-position are prepared by the methods summarized in Scheme IV. Intermediate (9) is oxidized by N-halosuccinimide reagents and the like to afford the 10-halo products (16). A final deprotection, if needed, then provides the final compounds (17). The 10-halo compounds (16) undergo displacement reactions with suitable nucleophilic reagents (step 2) to afford additional products (17a). A final deprotection, if needed, then provides the final compounds (17a). If desired, this methodology can be extended to the preparation of 10,10-disubstituted products. The 10-oxo product (18) is available by potassium persulfate oxidation of (9). Reduction of (18) gives 10-hydroxy compounds (16a, R^{IVb}=OH). A final deprotection of (18), if needed, provides the final compounds (19).

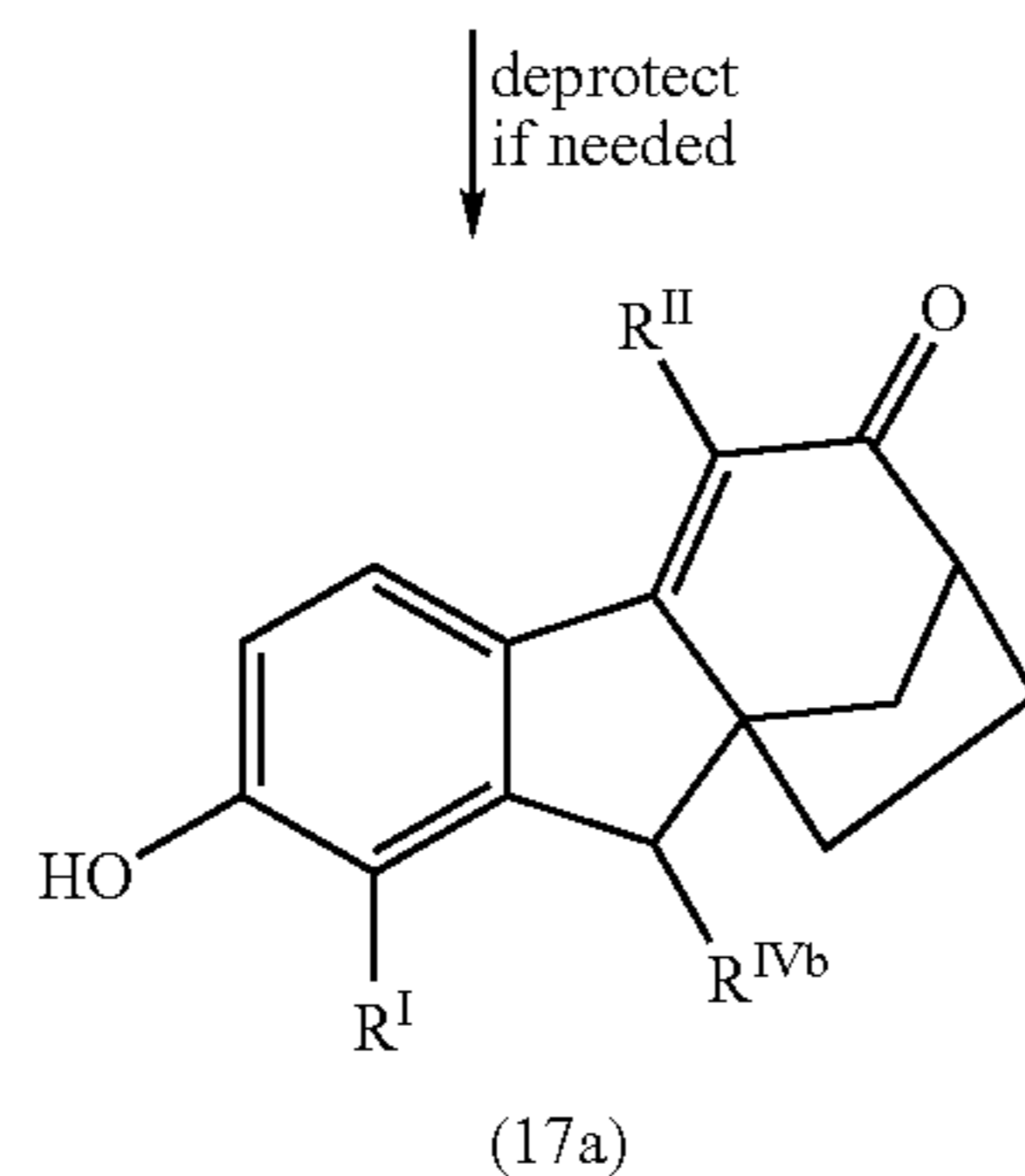
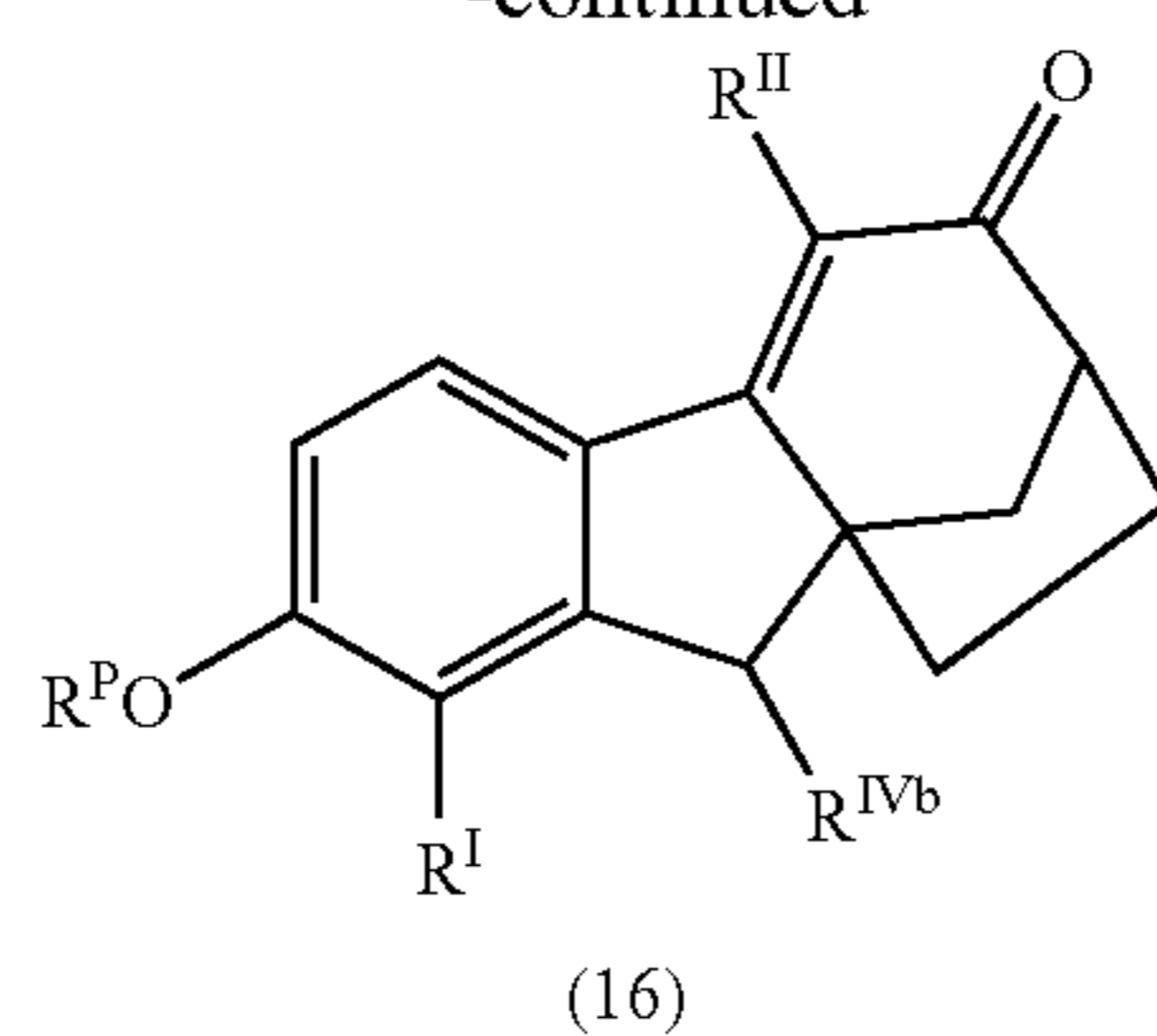
SCHEME IV



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-continued



Representative reagents and reaction conditions indicated in Scheme IV as steps 1–4 are as follows:

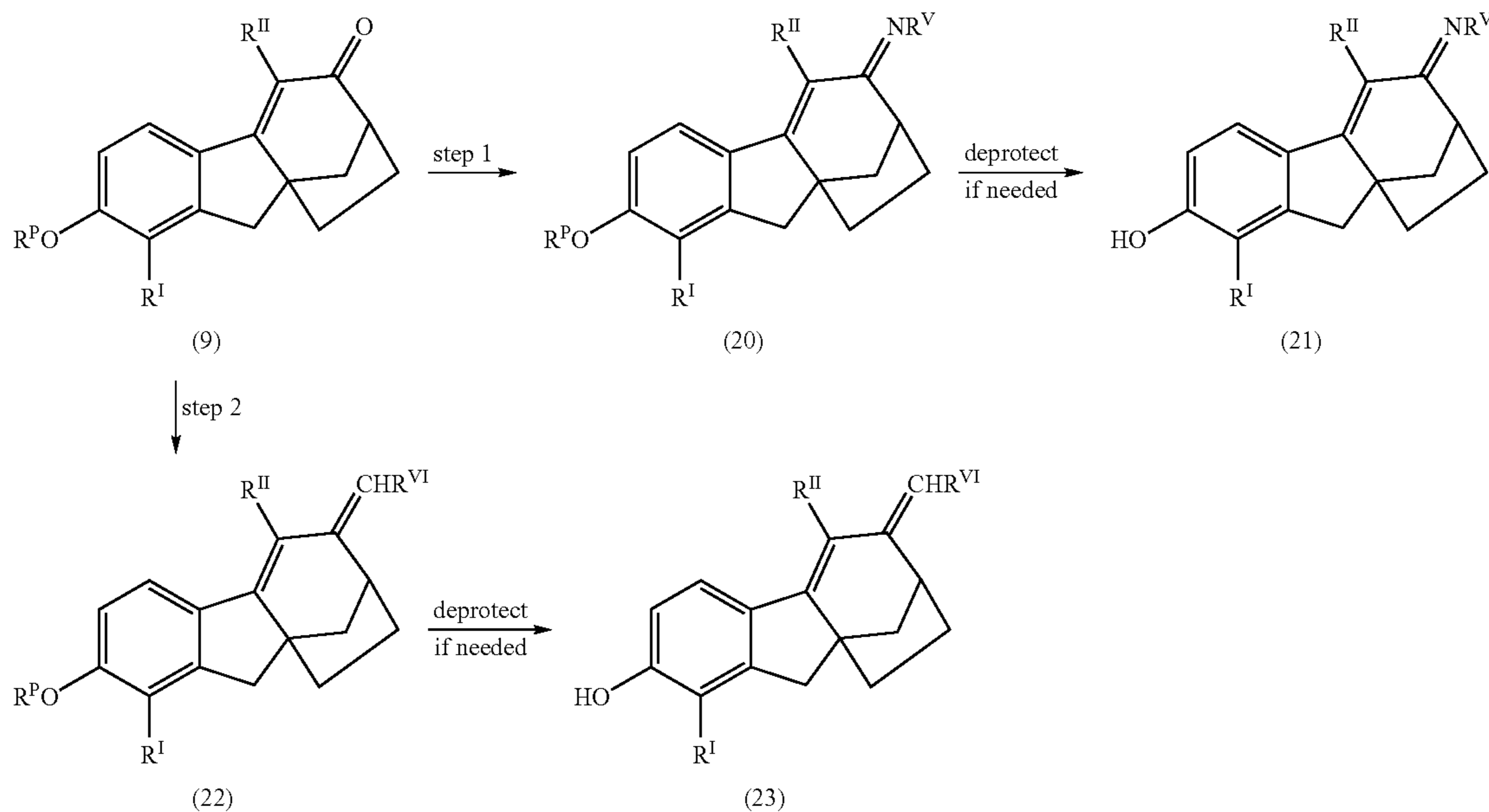
Step 1	NCS, AIBN or (PhCO) ₂ O ₂ , CCl ₄ , rt to 80° C.	R ^{IVa} = Cl
	NBS, AIBN or (PhCO) ₂ O ₂ , CCl ₄ , rt to 80° C.	R ^{IVa} = Br
Step 2	pyridine-HF, AgOTf, rt to 50° C.	R ^{IVb} = F
	AgOAc, HOAc, H ₂ O, rt to 100° C.	R ^{IVb} = OAc
	i) AgOAc, DMF, rt to 100° C.	R ^{IVb} = OH
	ii) NaOH, H ₂ O, MeOH	

-continued

Step 3	K ₂ S ₂ O ₈ , H ₂ O, MeCN, rt to 80° C.	
Step 4	NaBH ₄ , MeOH, 0° C. to rt	R ^{IVb} = OH

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Modifications of the C-6 ketone of (9) are outlined in Scheme V. In step 1, the ketone is reacted with a hydroxylamine, alkoxyamine or hydrazine reagent to give the 6-imino products (20). Ketone (9) also reacts with ylide reagents (step 2) to afford 6-alkylidene derivatives (22). Deprotection, if needed, provides the final products (21) and (23).

SCHEME V



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Representative reagents and reaction conditions indicated in Scheme V as steps 1 and 2 are as follows:

Step 1	$\text{NH}_2\text{OR}^a \cdot \text{HCl}$, pyridine, rt to 60° C.	$\text{R}^V = \text{OR}^a$
	$\text{NH}_2\text{NR}^a\text{R}^a$, EtOH, rt	$\text{R}^V = \text{NR}^a\text{R}^a$
Step 2	$\text{Ph}_3\text{P}^+\text{CH}_2\text{R}^{\text{VI}} \text{Br}^-$, BuLi, THF, 0 to 50° C.	

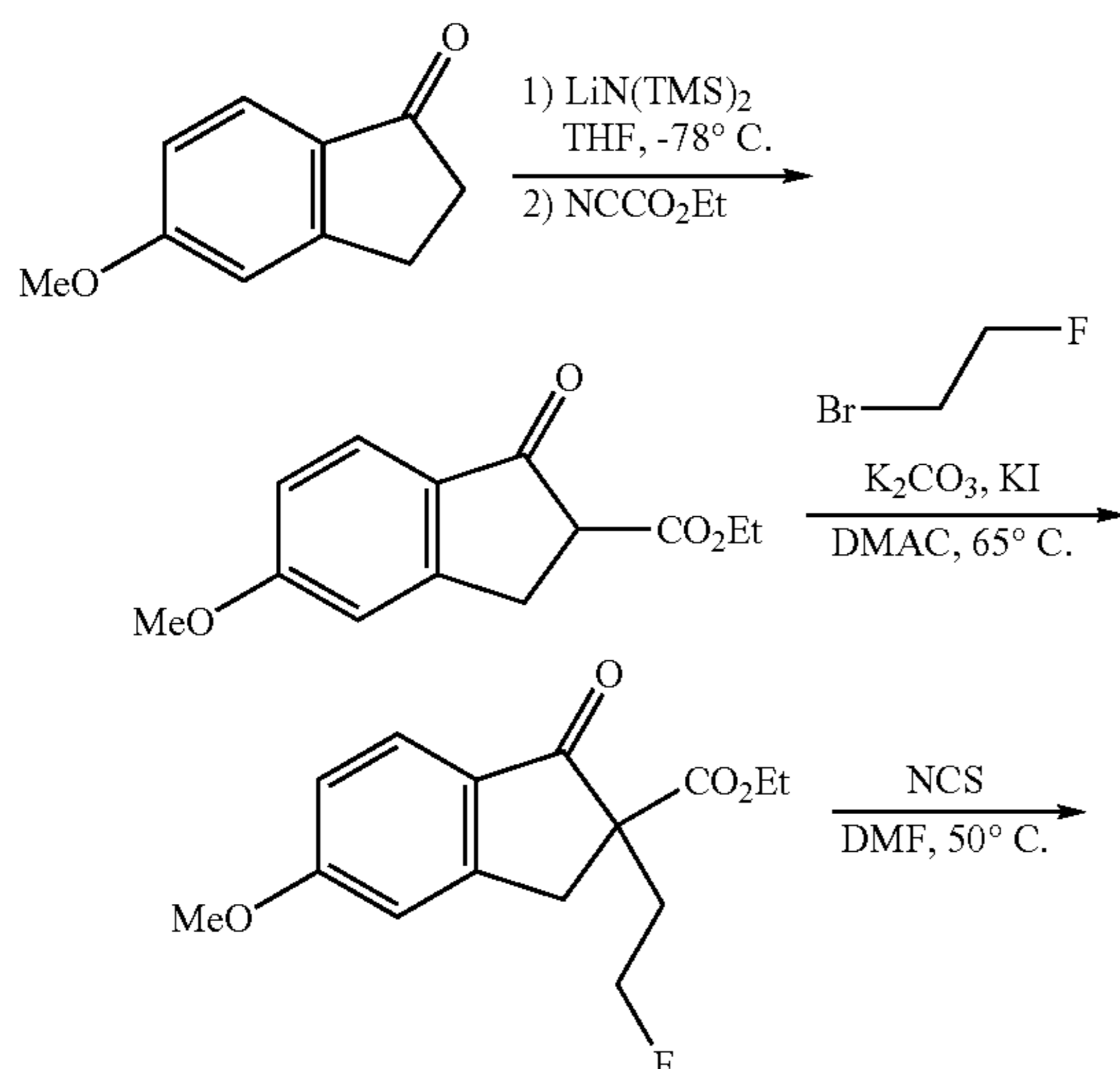
In Schemes I–V, the various R groups often contain protected functional groups which are deblocked by conventional methods. The deblocking procedure can occur at the last step or at an intermediate stage in the synthetic sequence. For example, if OR^P is a methoxyl group, it can be converted to a hydroxyl group by any of a number of methods. These include exposure to BBr_3 in CH_2Cl_2 at -78°C . to room temperature, heating with lithium chloride in DMF at 150°C ., heating with pyridine hydrochloride at $190\text{--}200^\circ\text{C}$., or treatment with EtSH and AlCl_3 in CH_2Cl_2 at 0°C . to room temperature. Another example involves the use of methoxymethyl (MOM) protection of alcohols and phenols. The MOM group is conveniently removed by exposure to hydrochloric acid in aqueous methanol. Other well known protection-deprotection schemes can be used to prevent unwanted reactions of functional groups contained in the various R substituents.

The final compounds prepared according to Schemes I–V have chiral centers and can be resolved into the separate enantiomers by known methods, for example by chiral HPLC. Separation into the individual enantiomers can also be accomplished at a number of intermediate stages in the synthesis. For example, in Scheme 1, separation into the individual enantiomers can be accomplished at the stage of compounds (6), (7), (8), (9), or (10).

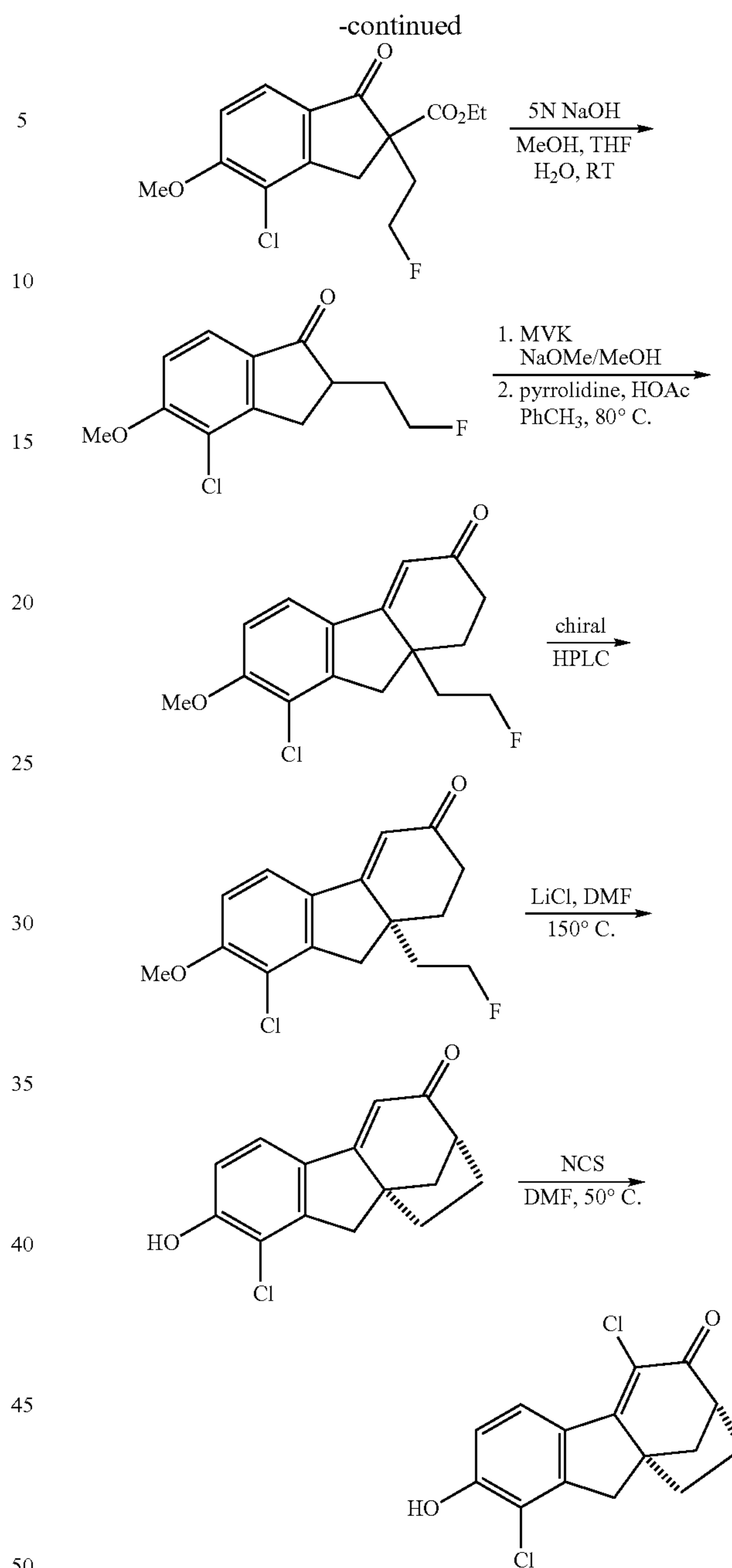
The following specific examples, while not limiting, serve to illustrate the methods of preparation of the compounds of the present invention.

EXAMPLE 1

Synthesis of (7-Beta, 9a-Beta)-1,5-Dichloro-2-Hydroxygibba-1,3,4a(10a),4b-Tetraen-6-one



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Step 1: ethyl 5-methoxy-1-oxoindane-2-carboxylate

To a solution of 5-methoxyindan-1-one (15.0 g, 92.5 mmol) in THF (370 mL) at -78°C . was added a 1.0 M solution of lithium bis(trimethylsilyl)amide in THF (200 mL, 200 mmol) via an addition funnel during 15 minutes. After 40 minutes, ethyl cyanofornate (14.0 mL, 142 mmol) was added during several minutes and the reaction mixture was allowed to warm gradually. After 30 minutes, the reaction mixture was partitioned between EtOAc and dilute aqueous HCl and the organic phase was washed with water and brine and dried over Na_2SO_4 . Filtration and removal of the solvent under reduced pressure gave ethyl 5-methoxy-1-oxoindane-2-carboxylate as a brown solid which was used in the next step without purification.

The reaction was repeated starting with 15.82 g (97.5 mmol) of 5-methoxyindan-1-one to give additional crude ethyl 5-methoxy-1-oxoindane-2-carboxylate.

Step 2: ethyl 2-(2-fluoroethyl)-5-methoxy-1-oxoindane-2-carboxylate

To a mixture of ethyl 5-methoxy-1-oxoindane-2-carboxylate (crude product from the preceding two reactions, ~190 mmol), K_2CO_3 (53.8 g, 389 mmol) and KI (64.7 g, 390 mmol) in anhydrous dimethylacetamide (792 mL) was added 1-bromo-2-fluoroethane (18.4 mL, 247 mmol) and the mixture was stirred and heated at 65° C. After 20 hours, analysis of an aliquot by NMR showed the reaction to be complete. After cooling to room temperature, most of the dimethylacetamide was removed by evaporation at reduced pressure. The residue was partitioned between EtOAc and water and the organic phase was washed with water (4 times) and brine and dried over Na_2SO_4 . Filtration and removal of the solvent under reduced pressure gave crude ethyl 2-(2-fluoroethyl)-5-methoxy-1-oxoindane-2-carboxylate which was used in the next step without purification.

Step 3: ethyl 4-chloro-2-(2-fluoroethyl)-5-methoxy-1-oxoindane-2-carboxylate

To a solution of ethyl 2-(2-fluoroethyl)-5-methoxy-1-oxoindane-2-carboxylate (44.6 g, 159 mmol) in DMF (159 mL) was added N-chlorosuccinimide (23.4 g, 175 mmol) in portions. The solution was heated at 50° C. and the reaction was monitored periodically by NMR analysis of aliquots. After 6 hours, the reaction was approximately 80% complete by NMR analysis. The reaction mixture was allowed to cool to room temperature and stand overnight. After reheating to 50° C., additional N-chlorosuccinimide (2.12 g, 15.9 mmol) was added. Monitoring by NMR was continued, and after 4.5 hours another portion of N-chlorosuccinimide (2.12 g, 15.9 mmol) was added. After another 3 hours, the reaction was allowed to cool to room temperature and stand overnight. Most of the DMF was removed by evaporation at reduced pressure and the residue was partitioned between EtOAc and water. The organic phase was washed with water (4 times) and brine and dried over Na_2SO_4 . Filtration and removal of the solvent under reduced pressure gave crude ethyl 4-chloro-2-(2-fluoroethyl)-5-methoxy-1-oxoindane-2-carboxylate. This material was used in the next step without purification.

Step 4: 4-chloro-2-(2-fluoroethyl)-5-methoxyindan-1-one

To a solution of ethyl 4-chloro-2-(2-fluoroethyl)-5-methoxy-1-oxoindane-2-carboxylate (56.4 g of crude product from the previous reaction) in THF (330 mL) was added methanol (50 mL) followed by a solution of methanol (116 mL)/water (166 mL). To the resulting clear red-orange solution was added SN aqueous NaOH (55.7 mL, 279 mmol) gradually during 9 minutes giving a black solution. After 3.5 hours, the reaction was quenched by addition of 12N aqueous HCl (30 mL, 360 mmol) and most of the THF and methanol were removed by rotary evaporation at reduced pressure. The residue was partitioned between EtOAc and water and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave crude product. Purification by flash chromatography on silica gel (elution with CH_2Cl_2) gave the product. Re-purification of mixed fractions gave additional product. The combined yield esd 4-chloro-2-(2-fluoroethyl)-5-methoxyindan-1-one which by NMR contained approximately 4% of the undesired 6-chloro-2-(2-fluoroethyl)-5-methoxyindan-1-one regioisomer.

Step 5: 8-chloro-9a-(2-fluoroethyl)-7-methoxy-1,2,9,9a-tetrahydro-3H-fluoren-3-one

To a suspension of 4-chloro-2-(2-fluoroethyl)-5-methoxyindan-1-one (18.0 g, 74.2 mmol) in methanol (250 mL) was added methyl vinyl ketone (7.7 mL, 92 mmol) during 2 minutes followed by addition of a 0.5 M solution of sodium methoxide in methanol (74.2 mL, 37.1 mmol). After 3 hours at room temperature, analysis of an aliquot by NMR and LC/MS showed the reaction to be complete. The dark reaction mixture was concentrated by rotary evaporation under reduced pressure. The residual oil was dissolved in toluene (980 mL) and acetic acid (6.4 mL, 112 mmol) was added followed by pyrrolidine (6.2 mL, 74.2 mmol). The resulting solution was heated at 80° C. for 3.25 hours and was then allowed to cool to room temperature and stand overnight. The reaction mixture was partitioned between EtOAc and water and the organic phase was washed successively with dilute aqueous HCl, dilute aqueous $NaHCO_3$ and brine. After drying over $MgSO_4$, filtration and evaporation gave crude product. Purification by flash chromatography on a column of 400 g of silica gel (elution with 5% EtOAc/ CH_2Cl_2) gave the product. Re-purification of some impure fractions gave additional product. The combined yield was 8-chloro-9a-(2-fluoroethyl)-7-methoxy-1,2,9,9a-tetrahydro-3H-fluoren-3-one which by NMR contained approximately 4% of the undesired 6-chloro-9a-(2-fluoroethyl)-7-methoxy-1,2,9,9a-tetrahydro-3H-fluoren-3-one regioisomer.

Step 6: Resolution of racemic 8-chloro-9a-(2-fluoroethyl)-7-methoxy-1,2,9,9a-tetrahydro-3H-fluoren-3-one by chiral HPLC

Racemic 8-chloro-9a-(2-fluoroethyl)-7-methoxy-1,2,9,9a-tetrahydro-3H-fluoren-3-one (17 g) was resolved by chiral HPLC on a Daicel Chiralcel OD column (elution with 15% EtOH:Heptane, fractions monitored at 220 nm). The pure fractions containing the first enantiomer to elute were combined and concentrated to give (9aR)-8-chloro-9a-(2-fluoroethyl)-7-methoxy-1,2,9,9a-tetrahydro-3H-fluoren-3-one as an oil which had a positive rotation. The fractions containing the second enantiomer to elute were combined and concentrated to give of (9aS)-8-chloro-9a-(2-fluoroethyl)-7-methoxy-1,2,9,9a-tetrahydro-3H-fluoren-3-one as an oil which had a negative rotation.

Step 7: (7beta,9abeta)-1-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one

To a mixture of (9aS)-8-chloro-9a-(2-fluoroethyl)-7-methoxy-1,2,9,9a-tetrahydro-3H-fluoren-3-one (5.34 g, 18.1 mmol) and lithium chloride (7.68 g, 181 mmol) was added DMF (102 mL) and the stirred suspension was heated to 150° C. giving a yellow solution. After 21 hours, the solution was cooled to room temperature and partitioned between EtOAc and 0.2N aqueous HCl. The organic phase was washed with water (4 times) and brine and dried over $MgSO_4$. Filtration and evaporation gave crude product. Purification by flash chromatography on silica gel (elution with 20% EtOAc/ CH_2Cl_2) gave (7beta,9abeta)-1-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one.

Step 8: (7beta,9abeta)-1,5-dichloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one

To a solution of (7beta,9abeta)-1-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one (3.51 g, 13.5 mmol) in DMF (54 mL) was added N-chlorosuccinimide (1.8 g, 13.5 mmol) and the reaction mixture was heated to 50° C. After 3 hours, NMR analysis of an aliquot showed the reaction to be complete. The reaction mixture was cooled to room tem-

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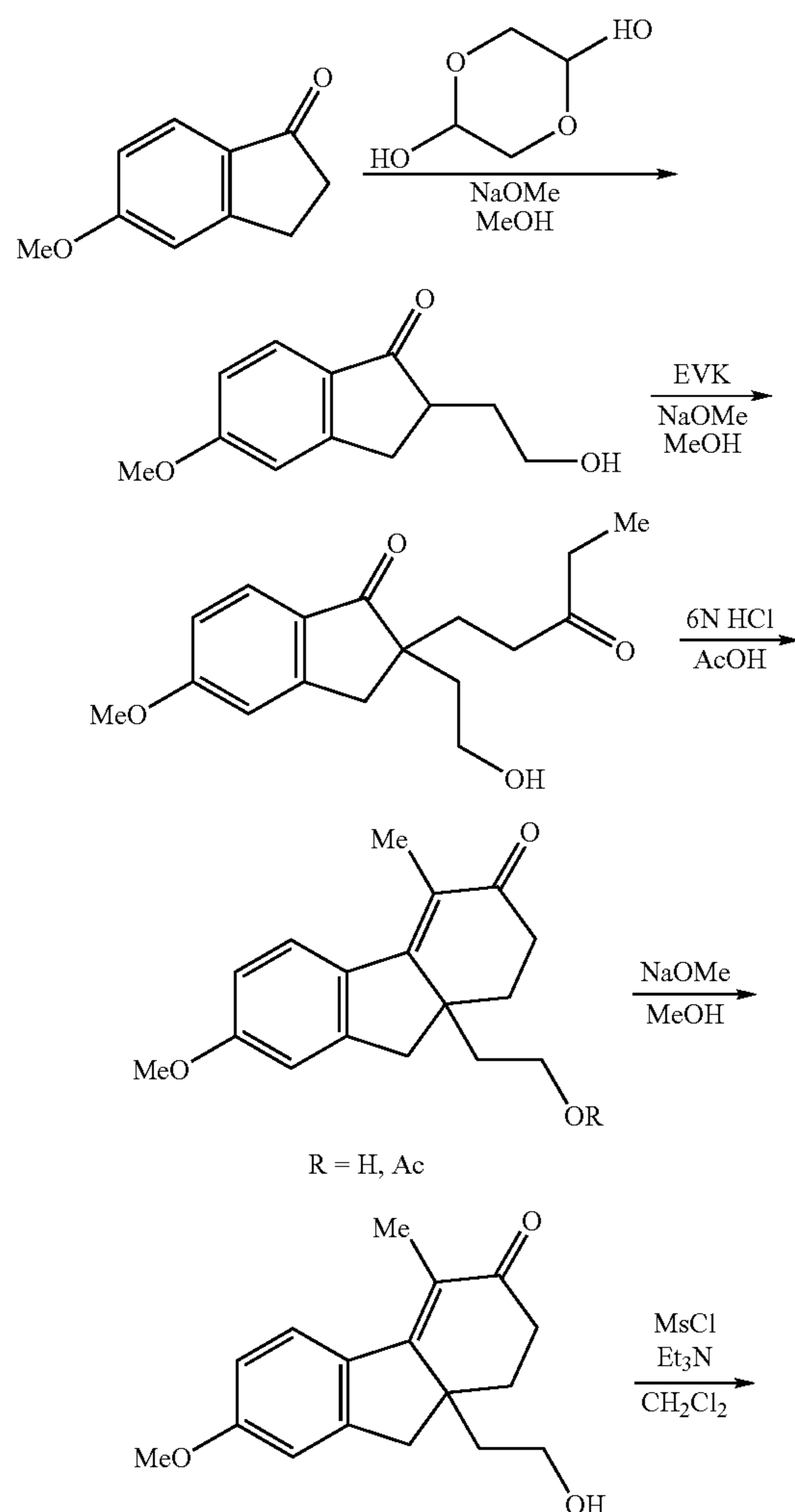
perature and partitioned between EtOAc and dilute aqueous HCl. The organic phase was washed with water (4 times) and brine and dried over $MgSO_4$. Filtration and evaporation gave crude product. Purification by flash chromatography was accomplished by pre-adsorbing a solution of the crude product in $MeOH/CH_2Cl_2$ onto silica gel. Elution of the column with 20% to 35% EtOAc/ CH_2Cl_2 gave the product as a solid which was dissolved in ethanol and precipitated with water. Filtration and evaporation under vacuum gave (7beta,9alpha)-1,5-dichloro-2-hydroxygibba-1,3,4a(10a), 4b-tetraen-6-one as a pale yellow powder.

1H NMR ($CDCl_3$, 500 MHz): δ 1.74–1.80 (m, 1H), 1.96–1.99 (m, 2H), 2.03 (dd, 1H), 2.13 (d, 1H), 2.33–2.40 (m, 1H), 3.17 (d, 1H), 3.25–3.30 (m, 1H), 3.32 (d, 1H), 6.01 (s, 1H), 7.09 (d, 1H), 8.25 (d, 1H).

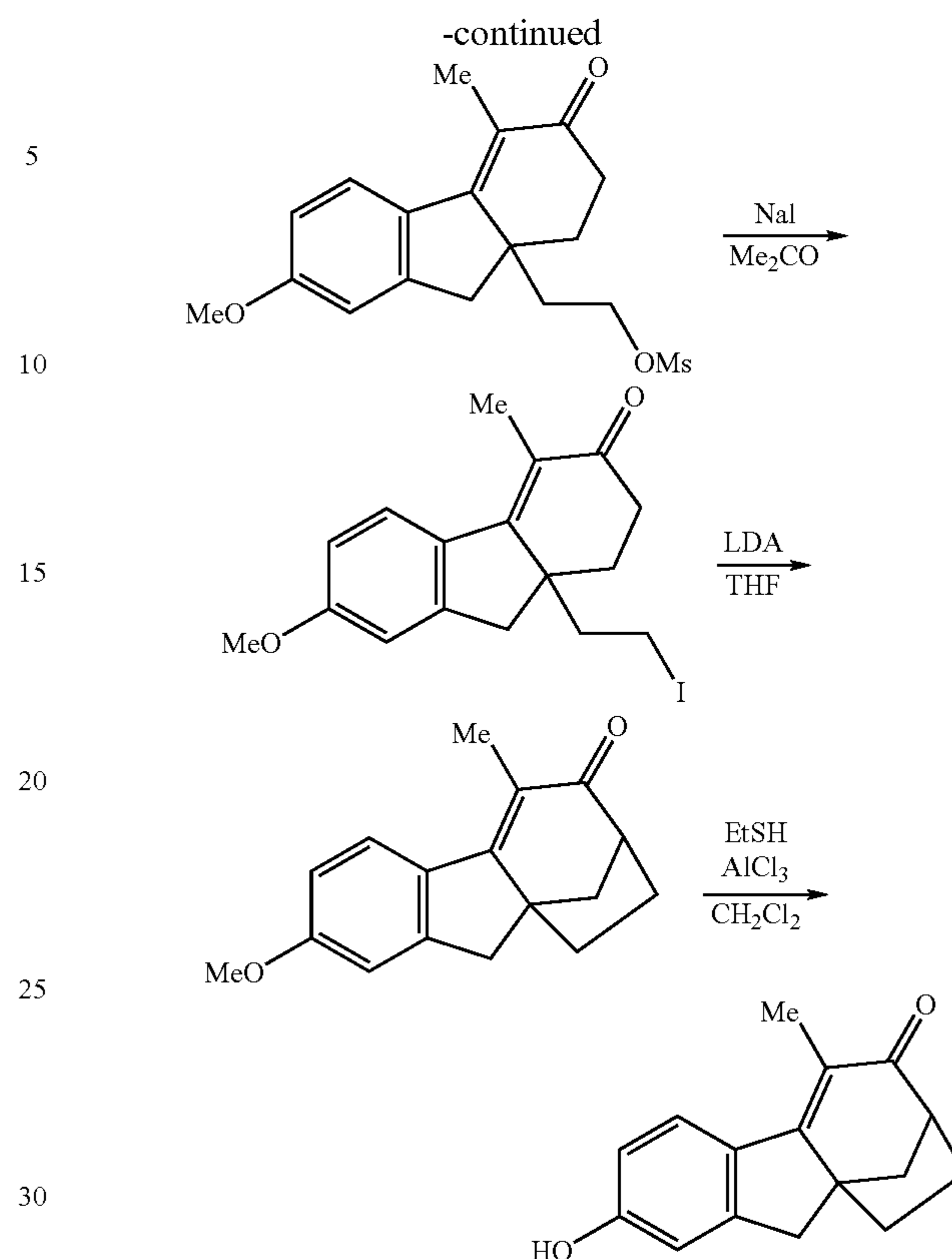
Mass spectrum: (ESI) $m/z=295$ (M+H).

EXAMPLE 2

Synthesis of 2-Hydroxy-5-Methylgibba-1.3.4a(10a), 4b-Tetraen-6-One



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Step 1: 2-(2-hydroxyethyl)-5-methoxy-1-indanone

A solution of 5-methoxy-1-indanone (500 mg, 3.08 mmol) in methanol (10 mL) was treated with 10% palladium on carbon (53 mg) followed by glycoaldehyde dimer (370 mg, 3.08 mmol) and 0.5M sodium methoxide in methanol (1.3 mL, 0.65 mmol). The mixture was placed under a hydrogen atmosphere (balloon) and stirred vigorously at room temperature for 65 hours. After purging with nitrogen, the mixture was filtered through a 0.45 μm Acrodisc and the disk was rinsed with methanol (2 mL). The filtrate was diluted with EtOAc (25 mL), washed with 0.1N HCl (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum to a solid. LC-MS of this material showed a mixture of starting material (major) and product.

The mixture was purified by chromatography on a Biotage Flash 12M KP-Sil column (12 mm \times 15 cm). The column was eluted with 3:2 EtOAc-hexanes, collecting 6 mL fractions every 30 sec. Fractions 20–36 were concentrated under vacuum and flashed with benzene to afford 2-(2-hydroxyethyl)-5-methoxy-1-indanone as an oil.

1H NMR ($CDCl_3$, 500 MHz) δ 1.80 and 2.05 (two m, CH_2CH_2OH), 2.79 and 3.35 (two dd, 3- CH_2), 2.83 (m, H-2), 3.77–3.90 (m, CH_2CH_2OH), 3.87 (s, OCH_3), 6.86 (d, H-4), 6.89 (dd, H-6), and 7.67 (d, H-7).

Step 2: 2-(2-hydroxyethyl)-5-methoxy-2-(3-oxopentyl)-1-indanone

A solution of 2-(2-hydroxyethyl)-5-methoxy-1-indanone (105 mg, 0.51 mmol) in methanol (2.0 mL) at room temperature was treated with ethyl vinyl ketone (EVK, 0.102 mL) and 0.5M sodium methoxide in methanol (0.204 mL, 0.1 mmol). The mixture was stirred in a capped flask and heated in an oil bath at 60 $^\circ$ C. for 8 hours. After cooling, the

reaction mixture was diluted with EtOAc (25 mL), washed with 0.2N HCl (15 mL), water (15 mL), and brine (15 mL), dried over MgSO₄, filtered, and evaporated under vacuum to afford 2-(2-hydroxyethyl)-5-methoxy-2-(3-oxopentyl)-1-indanone as an oil.

¹H NMR (CDCl₃, 500 MHz) δ 0.99 (t, COCH₂CH₃), 1.84–2.00 (m, CH₂CH₂OH and 2.28 (m, CH₂CH₂CO), 2.33 (m, COCH₂CH₃), 2.92 and 3.11 (two d, 3-CH₂), 3.63 and 3.72 (two m, CH₂CH₂OH), 3.87 (s, OCH₃), 6.86 (d, H-4), 6.91 (dd, H-6), and 7.67 (d, H-7).

Step 3: 9a-(2-hydroxyethyl)-7-methoxy-4-methyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one and 9a-(2-acetoxyethyl)-7-methoxy-4-methyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one

A solution of 2-(2-hydroxyethyl)-5-methoxy-2-(3-oxopentyl)-1-indanone (138 mg, 0.475 mmol) in acetic acid (3.0 mL) was diluted with aqueous 6N HCl (3.0 mL) and the resulting mixture was stirred and heated in an oil bath at 80° C. for 90 minutes. After cooling to room temperature, the reaction mixture was diluted with EtOAc (20 mL), washed with water (10 mL), 1M pH 7 phosphate buffer (15 mL), water (15 mL), and brine (15 mL), dried over MgSO₄, filtered, and evaporated under vacuum to an oil. LC-MS showed a mixture of 9a-(2-hydroxyethyl)-7-methoxy-4-methyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one and its O-acetyl derivative 9a-(2-acetoxyethyl)-7-methoxy-4-methyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one.

Step 4: 9a-(2-hydroxyethyl)-7-methoxy-4-methyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one

The mixture of products from step 3 was dissolved in methanol (5 mL) and the solution treated with 0.5M sodium methoxide in methanol (4.5 mL). The mixture was stirred at room temperature for 15 minutes then acidified with aqueous 2N HCl and concentrated under vacuum. The residue in EtOAc (25 mL) was washed with brine (20 mL), dried over MgSO₄, filtered, and evaporated under vacuum. The crude product was purified by chromatography on a Biotage Flash-12 M KP-Sil column (12 mm×15 cm). The column was eluted with 3:2 EtOAc-hexanes (145 mL) followed by 100% EtOAc, collecting 4 mL fractions every 30 seconds. Fractions 30–50 were combined and evaporated under vacuum to give the product as an oil. Treatment of this material with Et₂O gave the product 9a-(2-hydroxyethyl)-7-methoxy-4-methyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one as a solid.

¹H NMR (CDCl₃, 500 MHz) δ 1.72–1.86 (m, CH₂CH₂OH), 1.99 and 2.21 (two ddd, 1-CH₂), 2.04 (s, 4-CH₃), 2.45 and 2.63 (two ddd, 2-CH₂), 2.76 and 3.05 (two d, 9-CH₂), 3.47–3.62 (m, CH₂CH₂OH), 3.82 (s, OCH₃), 6.81–8.85 (m, H-6 and H-8), and 7.61 (d, H-5).

Step 5: 9a-[2-(methanesulfonyloxy)ethyl]-7-methoxy-4-methyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one

An ice-cold solution of 9a-(2-hydroxyethyl)-7-methoxy-4-methyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one (39 mg, 0.14 mmol) and triethylamine (0.030 mL, 0.21 mmol) in anhydrous dichloromethane (1.5 mL) was treated with methanesulfonyl chloride (0.014 mL, 0.18 mmol) and the resulting solution was stirred at 0° C. for 30 minutes. The mixture was diluted with EtOAc (10 mL), washed with water (5 mL), 0.2N HCl (5 mL), and brine (5 mL), dried over MgSO₄, filtered, and evaporated under vacuum to provide 9a-[2-(methanesulfonyloxy)ethyl]-7-methoxy-4-methyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one as an oil.

¹H NMR (CDCl₃, 500 MHz) δ 2.03 (m, CH₂CH₂O), 2.08 (s, 4-CH₃), 2.09 and 2.22 (two ddd, 1-CH₂), 2.53 and 2.61 (two ddd, 2-CH₂), 2.85 and 3.03 (two d, 9-CH₂), 2.89 (s,

SO₂CH₃), 3.85 (s, OCH₃), 4.03–4.17 (m, CH₂CH₂O), 6.86 (s, H-8), 6.87 (dd, H-6), and 7.64 (d, H-5).

Step 6: 9a-(2-iodoethyl)-7-methoxy-4-methyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one

A solution of 2-(2-methoxy-5-methyl-6-oxo-6,7,8,9-tetrahydro-8aH-fluoren-8a-yl)ethyl methanesulfonate (49.7 mg, 0.142 mmol) in acetone (2.0 mL) was treated with sodium iodide (85 mg, 0.57 mmol) and the resulting mixture was stirred and heated in an oil bath at 60° C. for 16 hours. After cooling, the mixture was diluted with acetone (2 mL) and filtered through a 0.45 μm Acrodisc filter. The filtrate was evaporated under vacuum and the residue in CH₂Cl₂ (3 mL) was re-filtered. The filtrate was purified by chromatography on a Biotage Flash 12M KP-Sil column (12 mm×15 cm) which was eluted with 4:1 hexanes-EtOAc, collecting 6 mL fractions every 30 seconds. Fractions 9–11 gave 9a-(2-iodoethyl)-7-methoxy-4-methyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one as an oil.

¹H NMR (CDCl₃, 500 MHz) δ 2.03 and 2.20 (two ddd, 1-CH₂), 2.08 (s, 4-CH₃), 2.24 (m, CH₂CH₂D), 2.51 and 2.61 (two ddd, 2-CH₂), 2.80 and 2.97 (two d, 9-CH₂), 2.85 and 2.95 (two m, CH₂CH₂I), 3.86 (s, OCH₃), 6.86 (br s, H-8), 6.87 (dd, H-6), and 7.64 (d, H-5).

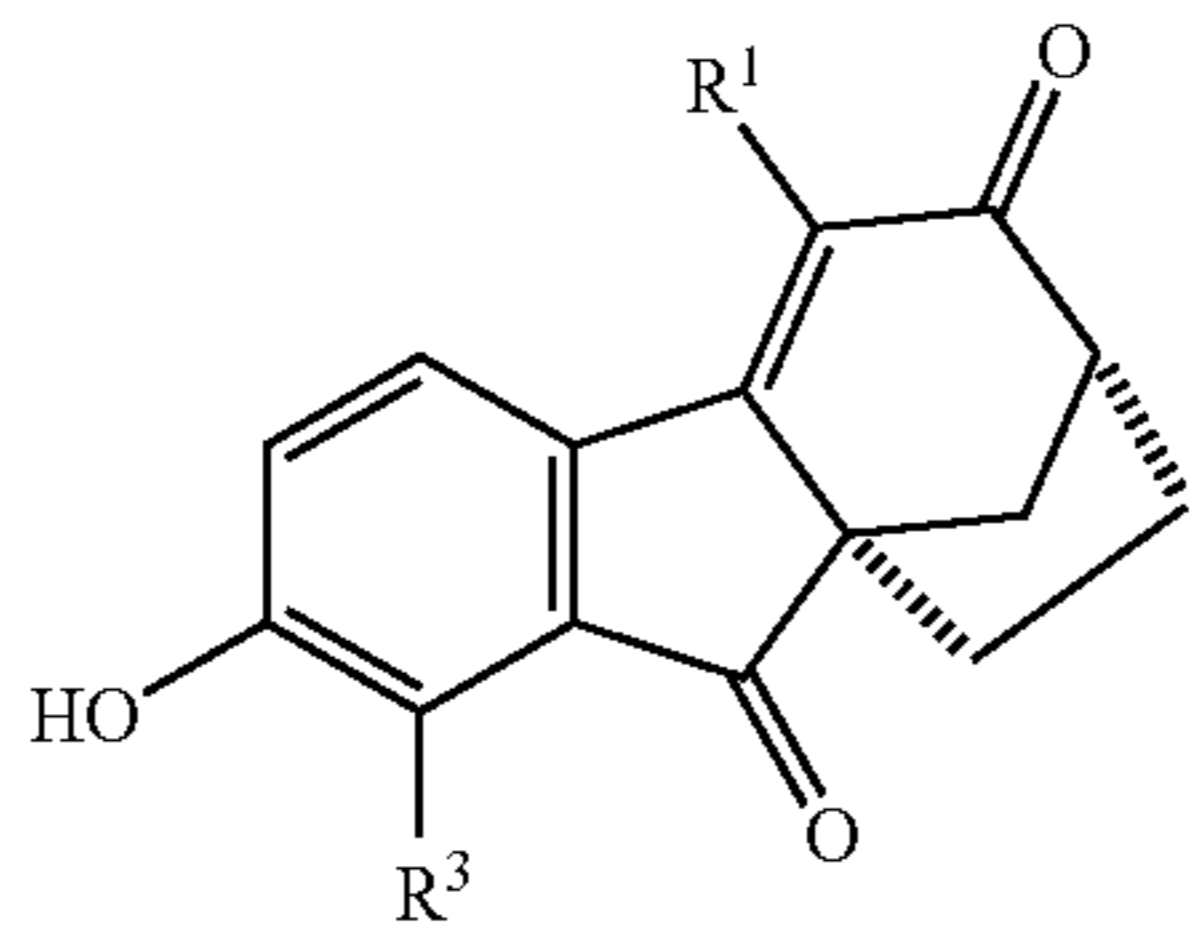
Step 7: 2-methoxy-5-methylgibba-1,3,4a(10a),4b-tetraen-6-one

A solution of N,N-diisopropylamine (0.015 mL, 0.107 mmol) in anhydrous tetrahydrofuran (THF, 1.0 mL) was placed under a nitrogen atmosphere, cooled in an ice bath, and treated with 1.6 M n-butyllithium in hexanes (0.061 mL, 0.098 mmol). The solution was stirred at 0° C. for 35 minutes, then cooled in a dry ice-acetone bath and, after aging for 5 minutes, treated with a solution of 9a-(2-iodoethyl)-7-methoxy-4-methyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one (34 mg, 0.089 mmol) in THF (1.0 mL). The reaction mixture was warmed from –78° C. to room temperature over 4 hours, stirred at room temperature for 21 hours, and then quenched with aqueous 2N HCl (0.5 mL) and diluted with EtOAc (10 mL). The organic phase was washed with water (5 mL) and brine (5 mL), dried over MgSO₄, filtered, and evaporated under vacuum to an oil. This material was purified by chromatography on a Biotage Flash 12M KP-Sil column (12 mm×15 cm), eluting with 6:1 hexanes-EtOAc and collecting 7 mL fractions every 30 seconds. Fractions 16–20 were combined and evaporated under vacuum to give a mixture of 2-methoxy-5-methylgibba-1(10a),2,4,4b-tetraen-6-one and the starting material 9a-(2-iodoethyl)-7-methoxy-4-methyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one as an oil.

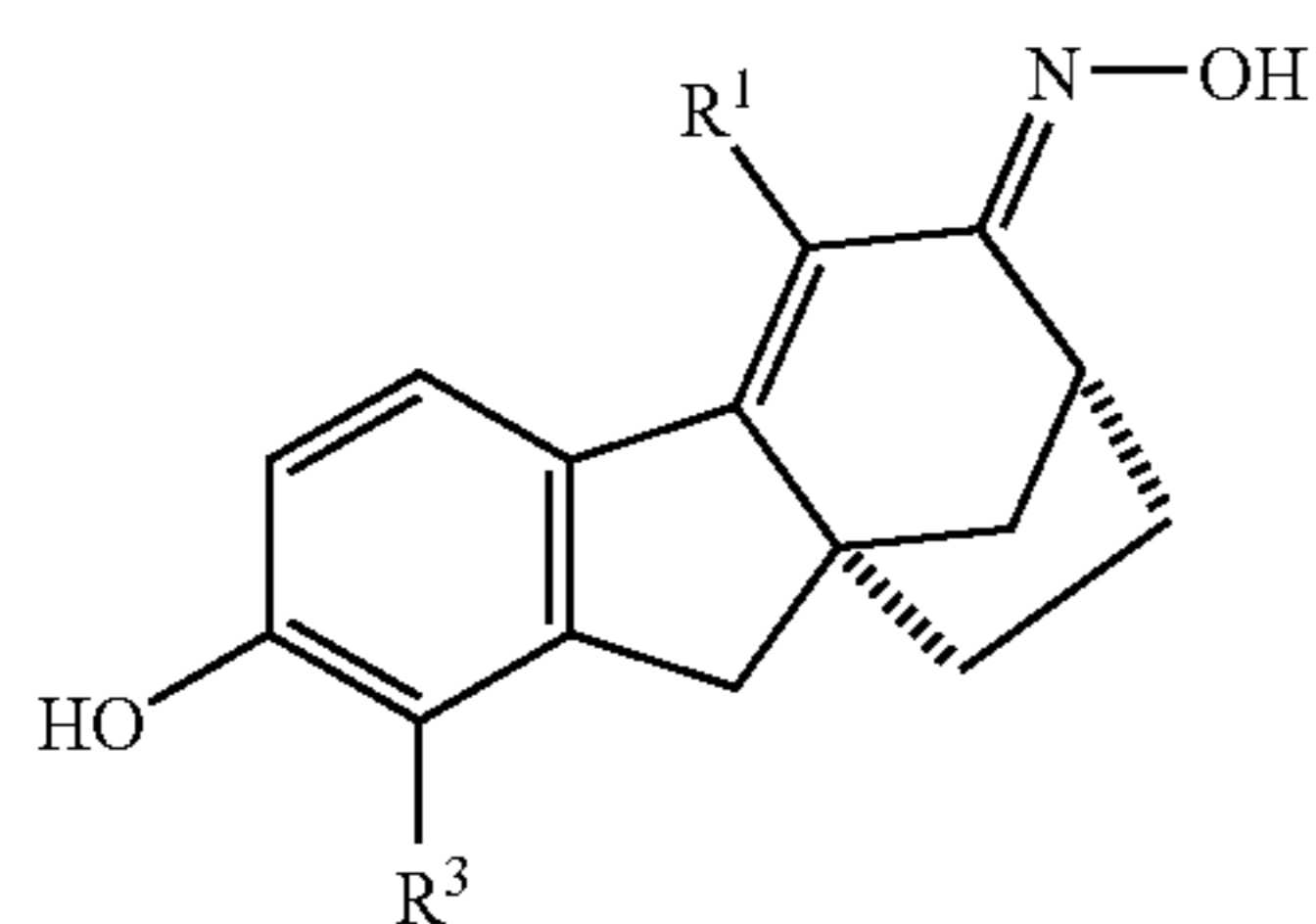
Step 8: 2-hydroxy-5-methylgibba-1,3,4a(10a),4b-tetraen-6-one

A solution of the product mixture from step 7 (21.7 mg, approx. 0.1 mmol) in anhydrous dichloromethane (1.0 mL) was treated at room temperature with aluminum chloride (75 mg, 0.56 mmol) and ethanethiol (0.032 mL, 0.43 mmol). After stirring at room temperature for 58 minutes, the yellow solution was treated with aqueous 2N HCl (1 mL) and EtOAc (9 mL), washed with water (4 mL) and brine (5 mL), dried over MgSO₄, filtered, and evaporated under vacuum to a solid film. The solid in warm EtOH (1 mL) was applied to two 0.1×20×20 cm silica gel GF plates which were developed with 1:1-hexanes-EtOAc. Two UV visible bands were removed, eluted with EtOAc, concentrated under vacuum, and the residues lyophilized from benzene containing some acetone. The band at R_f 0.47–0.57 gave mainly 2-hydroxy-

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- 19 R¹ = Cl (7beta,9alpha)-1,5-dichloro-2-hydroxygibba-
R³ = Cl 1,3,4a(10a),4b-tetraene-6,10-dione
¹H NMR (CDCl₃, 500 MHz): δ 1.85–1.98 (m, 2H), 2.10 (d, 1H),
2.27–2.34 (m, 2H), 2.39–2.47 (m, 1H), 3.44 (dd, 1H), 6.42 (bs, 1H), 7.51
(d, 1H), 8.51 (d, 1H).
 20 R¹ = Et (7beta,9alpha)-1-chloro-5-ethyl-2-hydroxygibba-
R³ = Cl 1,3,4a(10a),4b-tetraene-6,10-dione
¹H NMR (CDCl₃, 500 MHz): δ 1.13 (t, 3H), 1.75–1.85 (m, 2H), 1.96 (d,
1H), 2.19–2.26 (m, 2H), 2.33–2.40 (m, 1H), 2.62 (dt, 1H), 2.74 (dt, 1H),
3.24 (dd, 1H), 6.29 (s, 1H), 7.47 (d, 1H), 7.82 (d, 1H).



- 21 R¹ = Cl (7beta,9alpha)-1,5-dichloro-2-hydroxygibba-
R³ = Cl 1,3,4a(10a),4b-tetraen-6-one oxime
¹H NMR (CDCl₃, 500 MHz): δ 1.62–1.69 (m, 1H), 1.76–1.82 (m, 2H),
1.88 (dd, 1H), 1.86–1.95 (m, 1H), 2.19–2.26 (m, 1H), 3.06 (d, 1H), 3.21
(d, 1H), 4.11–4.14 (m, 1H), 6.91 (d, 1H), 8.03 (d, 1H).

Estrogen Receptor Binding Assay

The estrogen receptor ligand binding assays are designed as scintillation proximity assays employing the use of tritiated estradiol and recombinant expressed estrogen receptors. The full length recombinant human ER-α and ER-β proteins are produced in a baculoviral expression system. ER-α or ER-β extracts are diluted 1:400 in phosphate buffered saline containing 6 mM α-monothiolglycerol. 200 μL aliquots of the diluted receptor preparation are added to each well of a 96-well Flashplate. Plates are covered with Saran Wrap and incubated at 4° C. overnight.

The following morning, a 20 ul aliquot of phosphate buffered saline containing 10% bovine serum albumin is added to each well of the 96 well plate and allowed to incubate at 4° C. for 2 hours. Then the plates are washed with 200 ul of buffer containing 20 mM Tris (pH 7.2), 1 mM EDTA, 10% Glycerol, 50 mM KCl, and 6 mM α-monothiolglycerol. To set up the assay in these receptor coated plates, add 178 ul of the same buffer to each well of the 96 well plate. Then add 20 ul of a 10 nM solution of ³H-estradiol to each well of the plate.

Test compounds are evaluated over a range of concentrations from 0.01 nM to 1000 nM. The test compound stock solutions should be made in 100% DMSO at 100× the final concentration desired for testing in the assay. The amount of DMSO in the test wells of the 96 well plate should not exceed 1%. The final addition to the assay plate is a 2 ul

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aliquot of the test compound which has been made up in 100% DMSO. Seal the plates and allow them to equilibrate at room temperature for 3 hours. Count the plates in a scintillation counter equipped for counting 96 well plates.

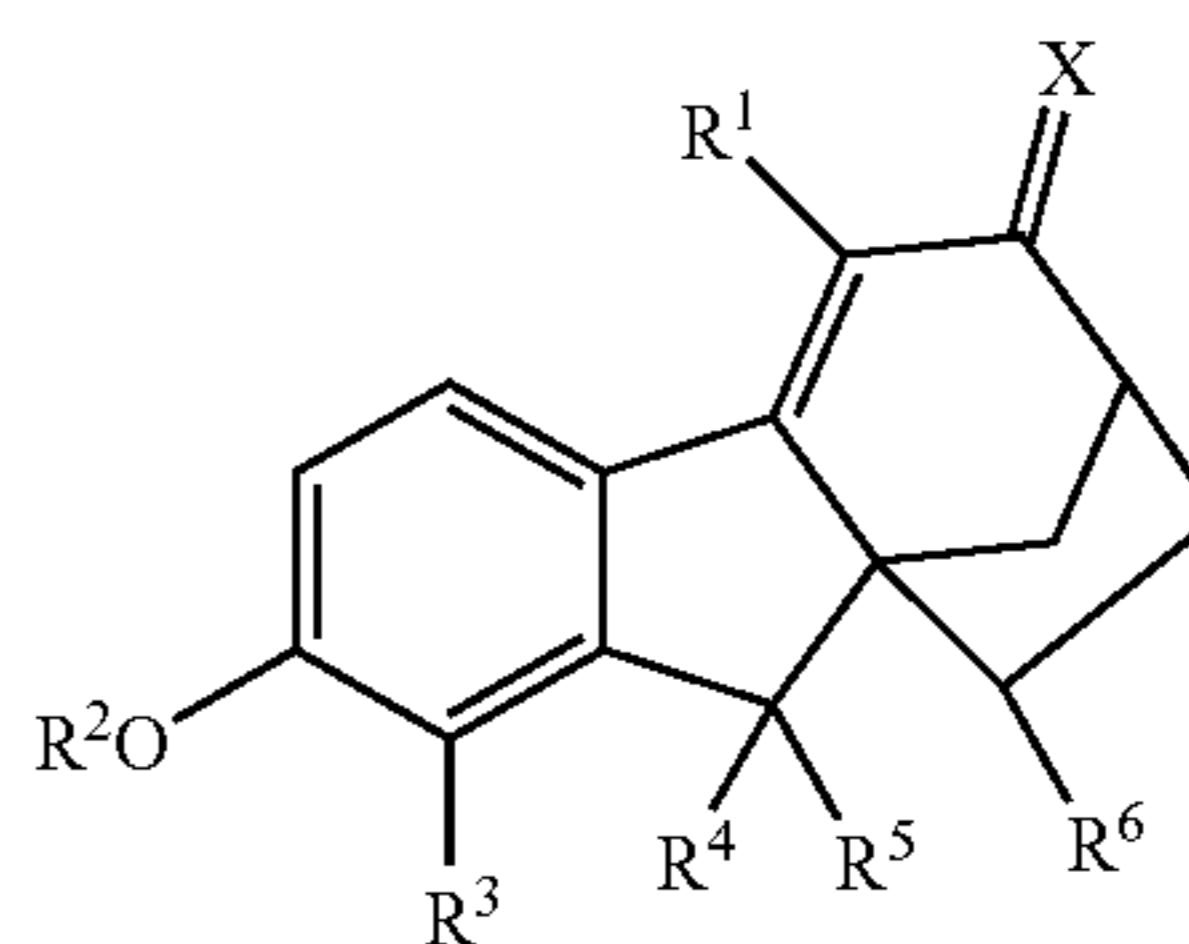
- 5 The compounds of Examples 1–21 exhibit binding affinities to the estrogen receptor α-subtype in the range of IC₅₀=54 to >1000 nm, and to the estrogen receptor β-subtype in the range of IC₅₀=1 to 33 nm.

Pharmaceutical Composition

- 10 As a specific embodiment of this invention, 25 mg of compound of Example 1, is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0, hard-gelatin capsule.

What is claimed is:

1. A compound of the formula:



- 25 wherein X is O, N—OR^a, N—N(R^a)₂, or C₁₋₆ alkylidene, wherein said alkylidene group is optionally substituted with hydroxyl, amino, O(C₁₋₄ alkyl), NH(C₁₋₄ alkyl) or N(C₁₋₄ alkyl)₂;

- 30 R¹ is fluoro, chloro, bromo, iodo, cyano, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, aryl, or heteroaryl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl groups are optionally substituted with one, two or three groups selected from the group consisting of fluoro, chloro, bromo, iodo, cyano and OR^a;

- 40 R² is hydrogen, R^a, (C=O)R^a or (C=O)OR^a;

- R³ is hydrogen, fluoro, chloro, bromo, iodo, C₁₋₂ alkyl, cyano or OR^a;

- R⁴ is hydrogen, fluoro, chloro, bromo or hydroxyl;

- R⁵ is hydrogen, fluoro, chloro, bromo or hydroxyl;

- 45 Or R⁴ and R⁵, when taken together with the carbon atom to which they are attached, form a carbonyl group;

- R⁶ is hydrogen, fluoro, chloro or C₁₋₅ alkyl, wherein said alkyl group is optionally substituted with a group selected from the group consisting of chloro, bromo, iodo, OR^a and 1–5 fluoro;

- 50 R^a is hydrogen, C₁₋₄ alkyl or phenyl, wherein said alkyl and phenyl groups are optionally substituted with a group selected from the group consisting of hydroxyl, amino, O(C₁₋₄ alkyl), NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)₂, chloro, bromo, 1–5 fluoro, iodo, cyano and OR^a; when two or more R^a groups are present, they are independently selected;

- 55 with the proviso that when R² and R⁶ are hydrogen, R¹ is not methyl; and when R⁶ is propyl, R¹ is not methyl, ethyl, bromo or trifluoromethyl;

or a pharmaceutically acceptable salt or stereoisomer thereof.

2. The compound of claim 1 wherein X is O; or a pharmaceutically acceptable salt or stereoisomer thereof.

3. The compound of claim 2 wherein R¹ is fluoro, chloro, bromo, iodo, cyano, C₁₋₄ alkyl or phenyl, wherein said alkyl and phenyl groups are optionally substituted with one, two

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or three groups selected from the group consisting of fluoro, chloro, bromo, iodo, cyano and OR^a; or a pharmaceutically acceptable salt or stereoisomer thereof.

4. The compound of claim 3 wherein R² is hydrogen; R⁴ is hydrogen; and R⁵ is hydrogen; or a pharmaceutically acceptable salt or stereoisomer thereof.

5. The compound of claim 4 wherein R⁶ is hydrogen or C₁₋₄ alkyl; or a pharmaceutically acceptable salt or stereoisomer thereof.

6. The compound of claim 1 which is

1,5-dichloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

2-hydroxy-5-(trifluoromethyl)gibba-1,3,4a(10a),4b-tetraen-6-one;

2-hydroxy-6-oxogibba-1,3,4a(10a),4b-tetraene-5-carbonitrile;

5-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

5-bromo-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

5-chloro-2-hydroxy-1-methylgibba-1,3,4a(10a),4b-tetraen-6-one;

5-bromo-2-hydroxy-1-methylgibba-1,3,4a(10a),4b-tetraen-6-one;

5-chloro-1-fluoro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

5-bromo-1-fluoro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

5-bromo-1-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

1-chloro-2-hydroxy-5-methylgibba-1,3,4a(10a),4b-tetraen-6-one;

1-chloro-5-ethyl-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

1-chloro-2-hydroxy-6-oxogibba-1,3,4a(10a),4b-tetraene-5-carbonitrile;

1-chloro-2-hydroxy-5-phenylgibba-1,3,4a(10a),4b-tetraen-6-one;

1-bromo-5-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

1,5-dibromo-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

2-hydroxy-5-methyl-9-propylgibba-1,3,4a(10a),4b-tetraen-6-one;

1,5-dichloro-2-hydroxygibba-1,3,4a(10a),4b-tetraene-6,10-dione;

1-chloro-5-ethyl-2-hydroxygibba-1,3,4a(10a),4b-tetraene-6,10-dione;

1,5-dichloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one oxime;

or a pharmaceutically acceptable salt or stereoisomer thereof.

7. The compound of claim 6 which is

(7beta,9alpha)-1,5-dichloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

(7beta,9alpha)-2-hydroxy-5-(trifluoromethyl)gibba-1,3,4a(10a),4b-tetraen-6-one;

(7beta,9alpha)-2-hydroxy-6-oxogibba-1,3,4a(10a),4b-tetraene-5-carbonitrile;

(7beta,9alpha)-5-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

(7beta,9alpha)-5-bromo-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

(7beta,9alpha)-5-chloro-2-hydroxy-1-methylgibba-1,3,4a(10a),4b-tetraen-6-one;

(7beta,9alpha)-5-bromo-2-hydroxy-1-methylgibba-1,3,4a(10a),4b-tetraen-6-one;

(7beta,9alpha)-5-chloro-1-fluoro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

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(7beta,9alpha)-5-bromo-1-fluoro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

(7beta,9alpha)-5-bromo-1-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

(7beta,9alpha)-1-chloro-2-hydroxy-5-methylgibba-1,3,4a(10a),4b-tetraen-6-one;

(7beta,9alpha)-1-chloro-5-ethyl-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

(7beta,9alpha)-1-chloro-2-hydroxy-6-oxogibba-1,3,4a(10a),4b-tetraene-5-carbonitrile;

(7beta,9alpha)-1-chloro-2-hydroxy-5-phenylgibba-1,3,4a(10a),4b-tetraen-6-one;

(7beta,9alpha)-1-bromo-5-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

(7beta,9alpha)-1,5-dibromo-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one;

(7beta,9beta,9alpha)-2-hydroxy-5-methyl-9-propylgibba-1,3,4a(10a),4b-tetraen-6-one;

(7beta,9alpha)-1,5-dichloro-2-hydroxygibba-1,3,4a(10a),4b-tetraene-6,10-dione;

(7beta,9alpha)-1-chloro-5-ethyl-2-hydroxygibba-1,3,4a(10a),4b-tetraene-6,10-dione;

(7beta,9alpha)-1,5-dichloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one oxime;

or a pharmaceutically acceptable salt or stereoisomer thereof.

8. A pharmaceutical composition comprising a compound of claim 1.

9. A pharmaceutical composition comprising a compound of claim 1 and another agent selected from the group consisting of an organic bisphosphonate; a cathepsin K inhibitor; an estrogen; an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent; calcitonin; Vitamin D; a synthetic Vitamin D analogue; a selective serotonin reuptake inhibitor; an aromatase inhibitor; or a pharmaceutically acceptable salt or mixture thereof.

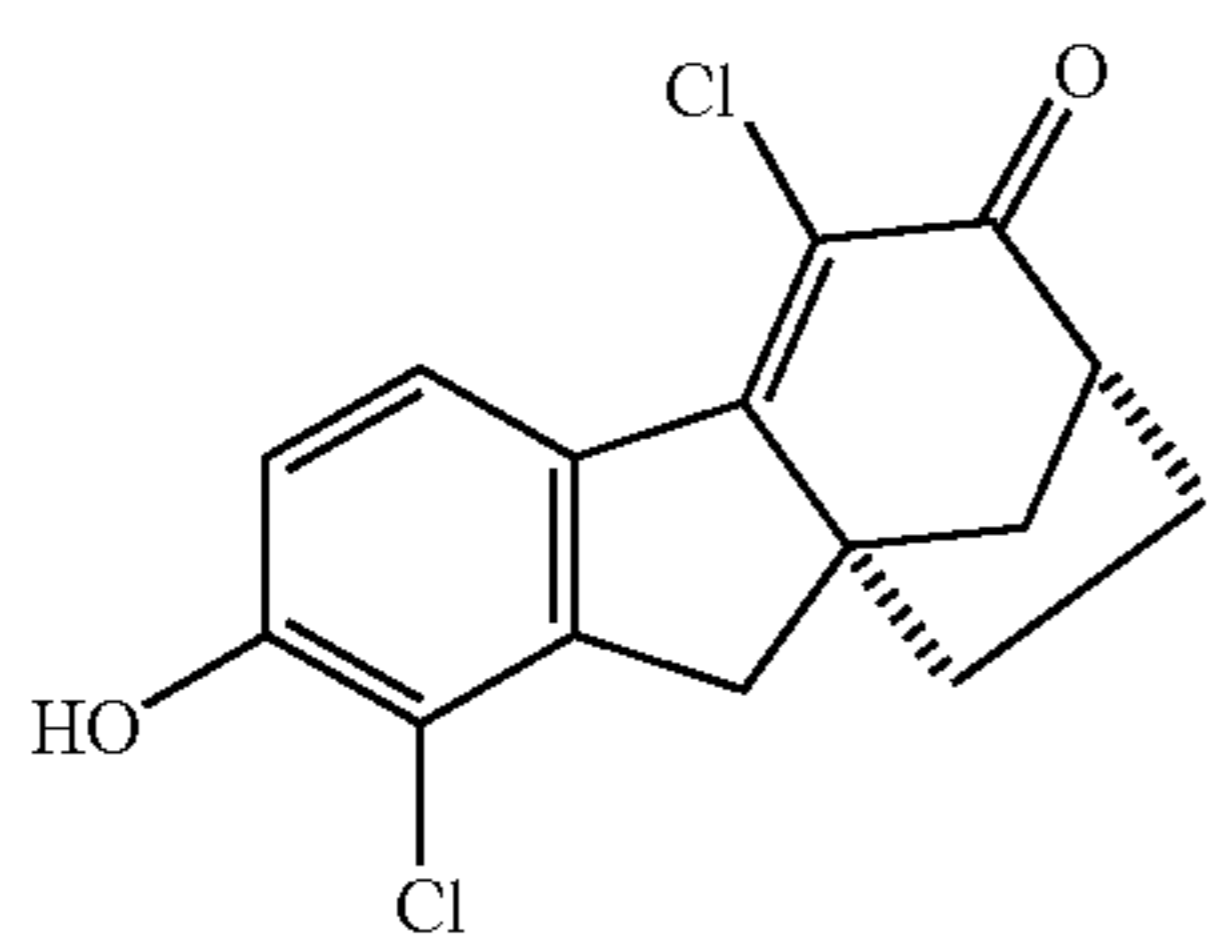
10. A method of treating bone loss, bone fractures, osteoporosis, metastatic bone disease, Paget's disease, periodontal disease, cartilage degeneration, endometriosis, uterine fibroid disease, hot flashes, cardiovascular disease, impairment of cognitive functioning, age-related mild cognitive impairment, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity, incontinence, anxiety, depression, perimenopausal depression, post-partum depression, premenstrual syndrome, manic depression, dementia, obsessive compulsive behavior, attention deficit disorder, sleep disorders, irritability, impulsivity, multiple sclerosis and Parkinson's disease, inflammation, inflammatory bowel disease, irritable bowel syndrome, sexual dysfunction, hypertension, retinal degeneration, an estrogen dependent cancer or prostate cancer in a mammal in need thereof by administering to the mammal a therapeutically effective amount of a compound according to claim 1.

11. A method of treating bone loss, bone fractures, osteoporosis, metastatic bone disease, Paget's disease, periodontal disease, cartilage degeneration, endometriosis, uterine fibroid disease, hot flashes, cardiovascular disease, impairment of cognitive functioning, age-related mild cognitive impairment, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell prolifera-

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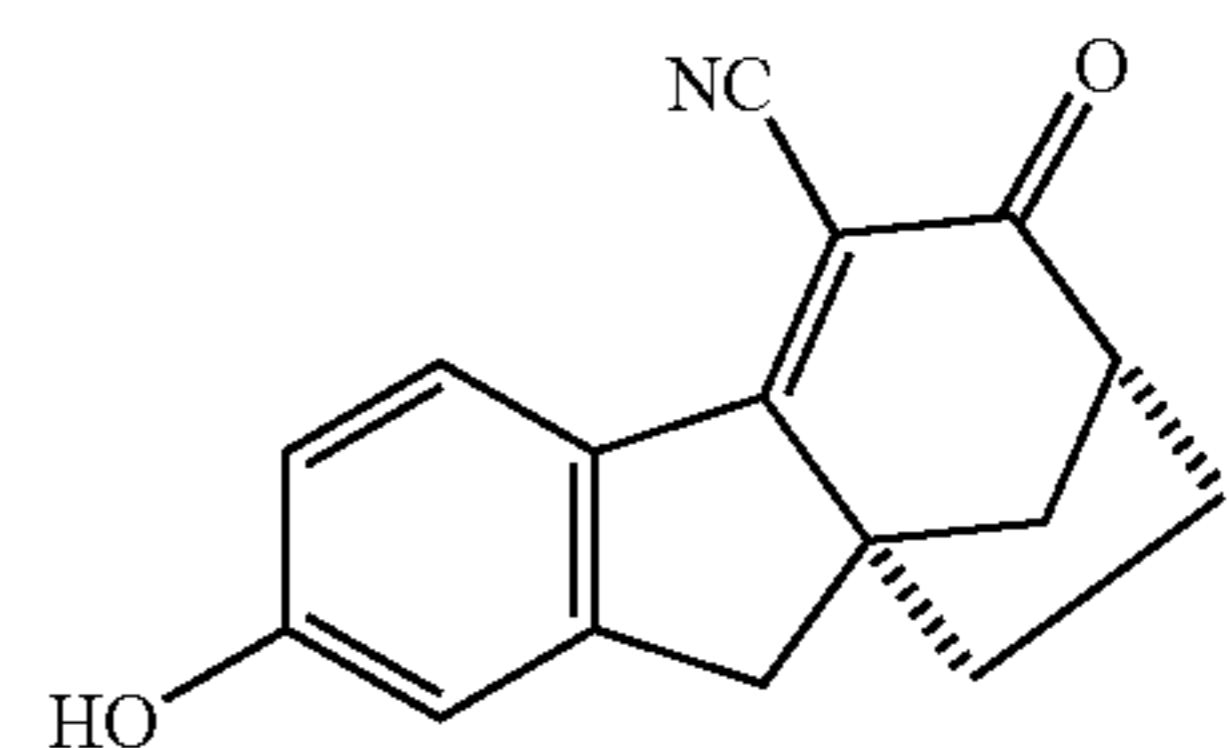
tion, obesity, incontinence, anxiety, depression, perimenopausal depression, post-partum depression, premenstrual syndrome, manic depression, dementia, obsessive compulsive behavior, attention deficit disorder, sleep disorders, irritability, impulsivity, multiple sclerosis and Parkinson's disease, inflammation, inflammatory bowel disease, irritable bowel syndrome, sexual dysfunction, hypertension, retinal degeneration, an estrogen dependent cancer or prostate cancer in a mammal in need thereof by administering to the mammal a therapeutically effective amount of a composition according to claim 9.

12. (7beta,9alpha)-1,5-dichloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one

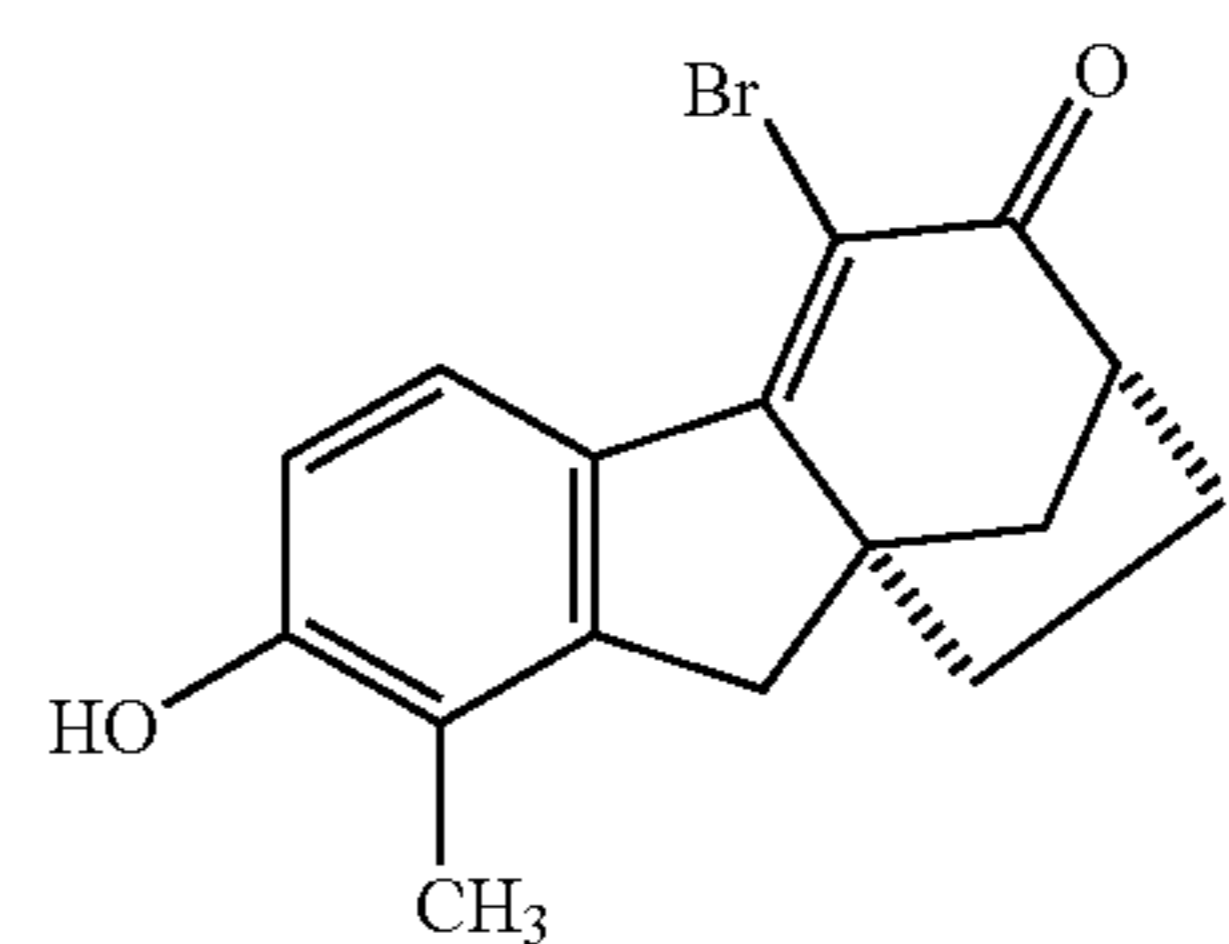


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13. (7beta,9alpha)-2-hydroxy-6-oxogibba-1,3,4a(10a),4b-tetraen-5-carbonitrile



14. (7beta,9alpha)-5-bromo-2-hydroxy-1-methylgibba-1,3,4a(10a),4b-tetraen-6-one



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